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FROM IMPROVED MANAGEMENT OF ACUTE PAIN

TO PREVENTION OF PERSISTENT POSTOPERATIVE PAIN

Elina Tiippana

ACADEMIC DISSERTATION

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The aim of the wise is not to secure pleasure, but to avoid pain.
- Aristoteles -

In memory of my Father Esko
and my Aunt Aune

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals:

I Tiippana E, Nilsson E, Kalso E. Post-thoracotomy pain after thoracic epidural analgesia: a prospective follow-up study. Acta Anaesthesiol Scand 2003; 47(4):433-8.

II Tiippana E, Bachmann M, Kalso E, Pere P. Effect of paracetamol and coxib with or without dexamethasone after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2008; 52(5):673-80.

III Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg 2007; 104(6):1545-56.

IV Tiippana E, Nelskylä K, Nilsson E, Sihvo E, Kataja M, Kalso E. Managing post-thoracotomy pain: epidural or systemic analgesia and the role of extended care – a randomized study with an "as usual" control group. *Submitted.*

V Tiippana E, Hamunen K, Kontinen V, Kalso E. The effect of paracetamol and tropisetron on pain: experimental studies and a review of published data. Basic Clin Pharmacol Toxicol 2013; 112(2):124-31.

ABBREVIATIONS

5-HT3	5-hydroxytryptamine-3
ASA	American Society of Anesthesiologists
APS	Acute pain service
BMI	Body mass index
CNS	Central nervous system
COX	Cyclo-oxygenase enzyme
CPM	Conditioned pain modulation
CPT	Cold pressor test
DNIC	Diffuse noxious inhibitory control
IASP	International Association for the Study of Pain
LCC	Laparoscopic cholecystectomy
NNH	Number-needed-to-harm = 1/ARR (ARR = absolute risk reduction for deterioration = CER-EER; CER = control event rate and EER = experimental event rate)
NNT	Number-needed-to-treat = 1/ARR (ARR = absolute risk reduction for improvement = CER-EER; CER = control event rate and EER = experimental event rate)
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OR	Operating room
PACU	Postanaesthesia care unit
PCA	Patient controlled analgesia
PCEA	Patient controlled epidural analgesia
POD	Postoperative day
PONV	Postoperative nausea and vomiting
PTPS	Post-thoracotomy pain syndrome
PVB	Paravertebral block
RCT	Randomized controlled trial
TEA	Thoracic epidural analgesia
VAS	Visual analogue scale
VRS	Verbal rating scale

ABSTRACT

Background and aims: Treating and preventing acute and persistent postoperative pain remains a challenge for health professionals. Patients are discharged to their homes far earlier than they previously have been, and pain management protocols are needed to accommodate this. After many types of operations, pain may persist for months in some patients and it is important to identify those patients at risk, treat their pain and to develop methods that decrease the incidence of persistent pain. One very painful operation with a high incidence of chronic pain is thoracotomy. As invasive pain management is not always possible, adjuvant drugs are an important component of multimodal analgesia. The main purpose of this study was to investigate the intensity of acute postoperative pain, the incidence of chronic pain after surgery, and to explore the possibilities of influencing these by focusing on thoracotomy and laparoscopic cholecystectomy (LCC) as examples. Another objective of this research was to assess the efficacy of opioid-sparing drugs, such as perioperative gabapentinoids, dexamethasone, NSAIDs and paracetamol in acute postsurgical pain management. This project also analyzed whether tropisetron abolishes the analgesic action of paracetamol.

Material and main methods: Studies I and IV included patients who were scheduled for thoracotomy for lung surgery. Study I (n=111) was a prospective, clinical follow-up study, and postoperative pain was treated with thoracic epidural analgesia (TEA, n=89), intravenous patient-controlled analgesia with oxycodone (IV-PCA, n=18) or with intramuscular opioids (n=4), providing all patients with regular NSAIDs/paracetamol. The patients' perioperative data were recorded and they were contacted 1 week, 3 months, and 6 months after discharge. Study IV was a prospective, randomized and partially double-blind clinical study enrolling 30 elective study patients (intervention group) and 111 standard care patients (control group). The intervention patients were divided into three groups (n=10 each): G1, perioperative diclofenac + IV-PCA morphine during pleural drainage + intercostal nerve block; G2, perioperative pare-/valdecoxib + IV-PCA morphine + ic-block; and G3, paracetamol + patient-controlled epidural analgesia (PCEA) with a background infusion of bupivacaine with fentanyl. The perioperative data were extensively recorded and the Study IV patients were contacted using the same procedure as in Study I. The control patients' data from the perioperative period were extracted, and a prospective follow-up questionnaire was mailed to the patients at six months after their surgery, and this procedure was similar to the questionnaire administered to the intervention group. Study II was double-blinded and 160 day-case LCC patients were randomized to 4 groups (n=40 each). Groups 1 and 3 received pare-/valdecoxib,

and Groups 2 and 4 paracetamol perioperatively and also at home for 7 days. In addition, Groups 3 and 4 were given dexamethasone intra-operatively. Study III was a systematic review with a meta-analysis including 22 randomized, controlled trials on the perioperative administration of gabapentin (21) and pregabalin (1) for postoperative pain relief. Study V consisted of 2 randomized, double-blind, crossover studies with 18 healthy male volunteers in each. The pain stimuli were the cold pressor test (CPT), contact heat pain (Study 1) and electrical stimulation (Study 2). Tropisetron 5 mg IV or saline were then administered, followed by paracetamol 2 g IV 30 min later. The individual changes in pain intensity and tolerance were recorded and also expressed as a percentage of the individual score at baseline. The literature on the interaction of paracetamol with setrons was subsequently reviewed.

Results: Thoracic epidural analgesia was especially effective in alleviating movement-related pain after thoracic surgery. One week after discharge, 92-100% of the patients needed daily pain medication and 71-77% required weak opioids. In Study I (TEA group), the incidence of chronic pain disturbing daily life at 6 months was 12%, and in Study IV, these numbers were 3% in the intervention group versus 24% in the control group ($p<0.01$). Diclofenac and valdecoxib provided similar analgesia and the groups were combined (Study IV). The duration of pain after coughing was shorter in the PCEA group than in the NSAID+IV-PCA group, and mechanical hyperalgesia was related to more pain when moving. Study II found that dexamethasone significantly reduced the need for oxycodone later in the Phase 2 postanaesthesia care unit (PACU) after LCC. The pain intensity was similar in all groups during the first week at home, but more patients in the coxib groups needed rescue medication than those in the paracetamol groups. Shoulder pain in all groups continued for several days postoperatively. The systematic review (Study III) indicated that pain relief was significantly better in the gabapentin groups. The consumption of opioids 24 h after a single dose of preoperative gabapentin 300-1200 mg was reduced by 20-62%, which is comparable to a reduction in morphine equivalent doses by 30±4 mg (mean±95% CI). Gabapentin also reduced opioid-related adverse effects, such as nausea, vomiting and urinary retention (NNTs 25, 6, and 7, respectively). In Study V, paracetamol 2 g IV did not display a statistically significant analgesia on the thermal (Study 1) or electrical pain stimulation tests (Study 2). After calculation of the sensory and pain scores, tropisetron seemed to amplify the analgesic action of paracetamol.

Conclusions: The extended protocol for pain management in hospital, which also covers the sub-acute phase at home, was found to be more important than any particular analgesic technique in itself in preventing acute and persistent post-thoracotomy pain. The value of a strict pain management protocol was also evident after LCC in the acute phase. An antiemetic technique + multimodal pain treatment with NSAIDs/paracetamol and dexamethasone enabled smooth outpatient LCC. The opioid-sparing and pain alleviating role of perioperative gabapentinoids was also demonstrated in a systematic review. However, the previously suggested interaction in which tropisetron abolished the analgesic action of paracetamol was not supported in an experimental volunteer study.

1. INTRODUCTION

The rapid development of surgery creates new challenges for the management of acute postoperative pain. According to the concept of fast-track surgery, patients are discharged much earlier than they have been previously and therefore the pain management protocols are needed to enable this. An unplanned overnight admission rate after a common day-case operation, a laparoscopic cholecystectomy (LCC), was 37% in a large Finnish study (1). Successfully conducted ambulatory surgery requires multimodal pain treatment, because poorly controlled pain and postoperative nausea and vomiting (PONV) are the most common reasons for delaying a patient's discharge home (2).

After several common operations, acute postoperative pain can be followed by persistent pain and for this reason, the ability to screen and treat the patients at risk is extremely important. The International Association for the Study of Pain (IASP) has defined persistent postoperative pain as a pain state that is apparent more than two months after surgery and that cannot be explained by other causes, such as a recurrence of disease, inflammation, etc. However, this definition is overly simplistic, because after undergoing some surgical procedures, an inflammatory response may continue far longer than three months (3). Since chronic pain can be severe in four to ten per cent of these patients, this represents a major clinical problem that is poorly recognized (4-7).

One of the most painful operations known is thoracotomy. The incidence of chronic post-thoracotomy pain after a year postoperatively is approximately 21-67%, and 3-5% of these patients suffer from severe disabling pain (8-14). The gold standard in managing post-thoracotomy pain has been thoracic epidural analgesia (TEA). However, TEA is an invasive method that can cause serious adverse effects, and technical failures are common. After Breivik et al. (15) published "Nordic Guidelines for Neuraxial Blocks in Disturbed Haemostasis", the feasibility of epidural analgesia diminished and the necessity increased for alternative methods that are less invasive.

The safety and efficacy of pain treatment is increased by using a combination of pharmacologically different analgesics. Opioid-sparing drugs are an important component of multimodal analgesia, which enables a reduction in opioid consumption as well as in the adverse effects that are opioid-induced. For example, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, gabapentinoids (16-21), and glucocorticoids, such as dexamethasone (22-26), are currently considered to be an integral part of the postoperative pain management.

Paracetamol was discovered over a century ago, but its mechanism of action remains a mystery. In experimental studies on rats, a specific 5-HT3 antagonist, intrathecal tropisetron, was reported to have abolished the antinociceptive action of

paracetamol (27, 28). Furthermore, in two studies on healthy volunteers, Pickering et al. (29, 30) reported the same interaction. This would suggest that paracetamol reinforces the descending serotonergic pathways that are involved in the pain inhibition in humans. Paracetamol is commonly used for postoperative and cancer-related pain, concomitantly with the setrons that prevent and manage the nausea and vomiting that are induced postoperatively and that follow chemotherapy treatment. Therefore, any recommendations regarding the co-administration of these drugs need to be based on strong evidence.

The main purpose of the present work was to investigate the intensity of acute postoperative pain, incidence of chronic pain after surgery as well as the possibility of influencing these with extended protocol for pain management, using thoracotomy and laparoscopic cholecystectomy as examples. Moreover, an analysis was conducted of the relevance of opioid-sparing drugs, such as gabapentinoids, corticosteroids, NSAIDs and paracetamol, in the treatment of acute postoperative pain. Additionally, one objective of this thesis is to offer some answers to the question of whether tropisetron interferes with the analgesic action of paracetamol.

2. REVIEW OF THE LITERATURE

2.1. CONSEQUENCES OF ACUTE POSTOPERATIVE PAIN

Even though surgical techniques have been developing continuously, acute postoperative pain remains a challenge. Poorly treated pain causes numerous adverse effects. For instance, endocrine responses include a burst of catabolic hormones and a reduction in anabolic hormones, and metabolic changes (31, Table 1). As a result, patients who suffer from acute postsurgical pain are susceptible to hypertension and to tachycardia and also have an increased risk of cardiac ischaemia and arrhythmias, diminished diuresis, reduced gastrointestinal motility and impaired immune function. In addition, due to the pain they are experiencing, patients are unable to cough effectively and this might cause pulmonary complications, particularly for those patients undergoing thoracic or upper abdominal surgery (32, 33). More attention needs to focus on the adequate management of acute postsurgical pain, because without it, the patients' recovery and discharge from hospital may be prolonged, and the consequence could be the human suffering.

Table 1. Metabolic and endocrine responses to injury. Adapted from Burton et al. (31).

Endocrine	↑ Catabolic hormones	↑ ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagon, cytokines (interleukins, TNF)
	↓ Anabolic hormones	↓ Insulin, testosterone
	Others	↑ β-endorphins, prolactin
Metabolic		
Carbohydrate	Hyperglycaemia, glucose intolerance, insulin resistance	↑ Glycogenolysis, gluconeogenesis (cortisol, glucagon, growth hormone, adrenaline, free fatty acids) ↓ Insulin
Protein	Muscle protein catabolism, ↑ acute phase proteins	↑ Cortisol, adrenaline, glucagons, interleukins, TNF
Lipid	↑ Lipolysis and oxidation	↑ Catecholamines, cortisol, glucagon, growth hormone

ACTH=adrenocorticotrophic hormone; ADH=antidiuretic hormone; TNF= tumour necrosis factor

2.2. FROM SINGLE MODE TO MULTIMODAL ANALGESIA IN PREVENTING AND TREATING ACUTE POSTOPERATIVE PAIN

Over 20 years ago, clinicians began to realize the value of the efficient treatment of postoperative pain by reducing the pain-related complications after surgery to facilitate earlier mobilization and rehabilitation. Since adequate pain relief cannot be achieved by a single agent or method without significant side effects, clinicians focused on combinations of analgesic drugs and methods (34). This focus occurred because acute postsurgical pain involves multiple mechanisms that ideally require a multimodal ("balanced") analgesia by combining drugs and techniques that act at different sites within the central and peripheral nervous systems. These additive or synergistic effects improve the analgesia and have opioid-sparing properties that decrease the opioid-related adverse effects (35-38). Multimodal analgesia was first described by Kehlet and Dahl (39), and this strategy is currently recommended for pain relief following both minor and major surgery (Figure 1).

One cause for the variable success of pharmacologic pain treatment is the different genetic disposition of the patients in terms of how much pain they perceive after encountering noxious stimuli or how they respond to analgesics. The patient's phenotype is regarded as being a result of the synergistic or antagonistic effects of several genetic polymorphisms. These polymorphisms modulate the perception of pain. They also alter the pharmacokinetic mechanisms that control the availability of active analgesic molecules as well as the pharmacodynamic interactions of analgesics with their target receptors. With the complex nature of pain involving various mechanisms, a multigenic approach to genetics could be required to tailor individualized pain therapy to the patient's genotype (40). For example, the natural variation in the μ-opioid gene *OPRM1* may predict increased pain and analgesic use following thoracotomy (41), and research suggests that the catechol-*O*-methyltransferase gene (*COMT*) modulates opioid activity and associates with postsurgical pain intensity (42). However, many other factors, such as environment and the patient's psychologic vulnerability, expressed as catastrophising and anxiety, also affect the patient's pain experience. Therefore, methods such as patient-controlled analgesia (PCA) could be useful to enable the patients to modulate their own pain treatment, taking account of their individual need for analgesics.

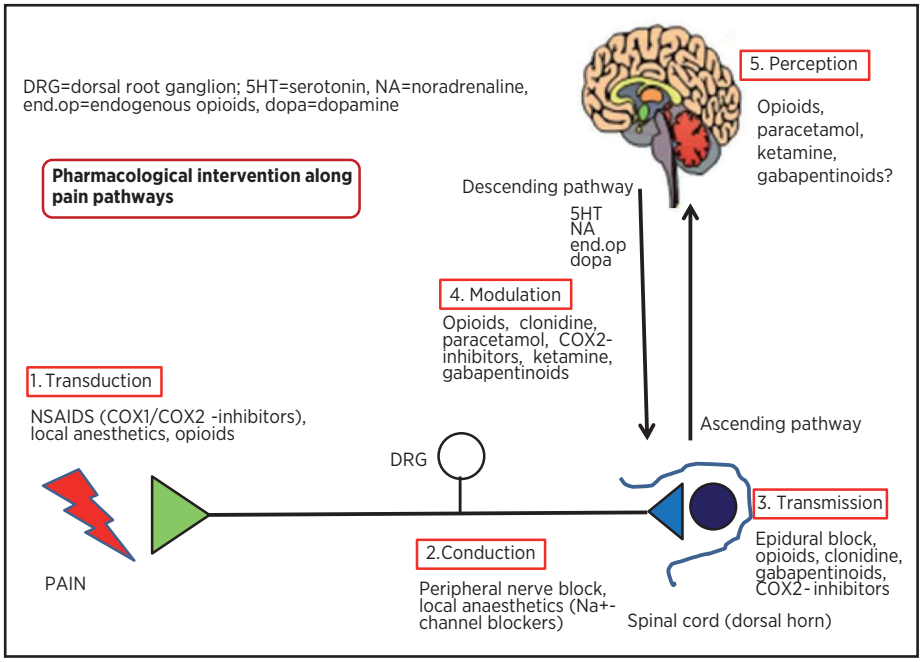


Figure 1. Multimodal approach to acute pain management. Adapted from Chandrakantan et al. (36).

2.2.1. OPIOIDS

For the treatment of moderate to severe postoperative pain, opioids are still the mainstay of systemic analgesia. Of all opioids, morphine remains the standard against which the other opioids are compared. One of its metabolites, morphine-6-glucuronide (M6G), contributes to analgesia and to adverse effects (43). Another mu-opioid receptor (OPR) -agonist, oxycodone, is more potent than morphine, which could be explained by an active transport system through the blood brain barrier (44). In addition, intravenous fentanyl has a fast onset of action and a lack of active metabolites, and it is commonly used perioperatively and in the postanaesthesia care unit (45). In comparison, the opioids that are not commonly used for acute postsurgical pain in Finland are hydromorphone, pethidine and buprenorphine (an agonist-antagonist).

Strong opioids may be administrated orally, intravenously, intramuscularly, subcutaneously, via neuraxial (epidural or intrathecal), intranasal or peripheral routes. Particularly morphine and oxycodone may be administered via intravenous patient controlled analgesia (IV-PCA) device (46), which provides better analgesia than the conventional parenteral opioid regimens. In a clinical setting, patients who were given IM opioid analgesics were more than twice as likely to experience moderate to severe pain as those who were given IV-PCA (47). For example, Ballantyne et al. (48) reported a non-significant trend towards lower opioid use in PCA patients, but studies published since then have reported conflicting results

(49). In a Cochrane review, IV-PCA led to higher opioid consumption but was still safe if background infusion was not used and if the patients were carefully observed (50). It is possible that the difference in opioid consumption may not reflect a true difference between the analgesic regimens, but may simply be due to, for instance, nurse availability or be a result of the nurse's assessment of pain and need for opioid administration. Pettersson et al. (51) found that pain relief after cardiac surgery using IV-PCA was comparable to the nurse-managed IV opioids while patients were in an intensive care unit where the nurse: patient ratio was 1:1. However, when the patients were transferred to a general ward, significantly better analgesia was achieved with PCA.

The neuraxial administration of opioids is based on spinally mediated analgesia via the presynaptic and postsynaptic receptors in the substantia gelatinosa in the dorsal horn. Neuraxial opioids also potentiate the descending inhibition from the μ-opioid receptor activation in the periaqueductal area of the brain (52). When intrathecally administered, hydrophilic opioids, such as morphine, have a slower onset of action and have longer half-lives in the cerebrospinal fluid with greater spinal cord bioavailability and cephalad migration as compared to the lipophilic opioids, such as fentanyl. A meta-analysis (53) reported a greater risk of respiratory depression as well as of nausea and vomiting with intrathecal morphine doses of 300 μg or more compared to lower doses. Furthermore, when epidurally administered, hydrophilic morphine has the slowest onset and offset of action and the highest bioavailability in the spinal cord (54). However, evidence is conflicting as to whether epidural fentanyl acts via spinal absorption rather than via systemic absorption (54, 55, 56). An infusion of epidural fentanyl appears to produce analgesia by uptake into the systemic circulation, whereas a bolus dose of fentanyl acts via a selective spinal mechanism (57). The adverse effects caused by systemic opioids may be reduced by the epidural administration of opioids, and a significant improvement has been demonstrated in postoperative analgesia and a reduction in motor blockade when opioids are added to epidural local anaesthetics (58, 59).

Tramadol is a weak opioid agonist and a serotonin as well as a noradrenaline reuptake inhibitor, and it is also effective in the treatment of neuropathic pain. As a sole agent, tramadol may not provide adequate pain relief for moderate or severe acute postsurgical pain (60). Ten per cent of another weak opioid, codeine, is metabolized to morphine. The analgesic action of codeine also depends on the patient's metabolic activity of the CYP2D6 cytochrome P450 isoenzyme. For example, poor metabolisers (8-10% of Caucasians) do not benefit from codeine, and ultra-rapid metabolisers (3-5%) generate significantly higher levels of morphine (61). Furthermore, codeine is available only in a peroral combination with paracetamol or ibuprofen.

Opioids also have dose-related adverse effects, such as respiratory depression, sedation, pruritus, nausea and vomiting, a slowing of the GI function and urinary

retention. For these adverse effects, therefore, opioid-sparing drugs and analgesic techniques are recommended (62). The incidence of some common adverse effects of opioids is presented in Table 2. After colon surgery, the incidence of postoperative ileus varies from 3% to 24%, depending on the amount of opioids administered postoperatively (63). However, one drawback is that treatment with opioids may lead to both opioid-tolerance (a desensitization of antinociceptive pathways to opioids) and paradoxically, to opioid-induced hyperalgesia (OIH), which is a sensitization of the pronociceptive pathways, leading to pain hypersensitivity. These phenomena can significantly reduce the analgesic effect of opioids. The mechanisms underlying the development of tolerance and OIH are thought to include the activation of the central glutaminergic system via the NMDA receptor, as well as other transmitter and receptor systems (64-66).

Opioids may also be involved in tumour growth. Recent epidemiologic studies indicate a positive association between administering perioperative opioid and tumour progression. For example, Lennon et al. (67) demonstrated that the overexpression of the opioid receptors in a human non-small cell lung cancer cell line increased tumour growth and metastasis, supporting the role of opioid receptor activation in tumour progression. Furthermore, breast cancer-specific mortality was significantly reduced in patients who had a genetic variant in the μ-opioid receptor that reduces opioid response (68). Clinical studies on the immunosuppressive effects of opioids during surgery are complex because pain itself may suppress immunity by producing endogenous opioids. Nonetheless, the use of regional anaesthetics is recommended to minimize immunosuppression. Moreover, the possible therapeutic role of peripherally restricted μ-opioid antagonists (for example, methylnaltrexone) on cancer growth and metastasis also deserve further study (69).

Table 2. Incidence of common adverse effects of opioids for postoperative pain. Adapted from Dolin & Cashman (62), Hudcova (50) and Barletta (63).

Adverse effect	IM opioids	iv-PCA opioids	Epidural opioids
Respiratory depression (respiratory rate <10 bpm)	1%	1%	1%
Nausea	17%	32%	19%
Vomiting	22%	21%	16%
Pruritus	3%	14%	16%
Excessive sedation*	5%	5%	1%
Urinary retention	15%	13%	29%

IM=intramuscular; bpm=breaths per minute; excessive sedation="oversedated, deeply asleep/ hard to rouse", VAS >3/10.
Greater incidence of nausea and pruritus with iv-PCA compared to IM-opioids may be due to higher opioid consumption with iv-PCA
(Hudcova 2006).

2.2.2. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Cyclooxygenase (COX) is an enzyme responsible for the formation of important biological mediators called prostanoids, including prostaglandins, prostacyclin and thromboxane. At present, two COX isoenzymes are known: COX-1 and COX-2 (Figure 2). Non-selective NSAIDs (for example, diclofenac, ketoprofen, ketorolac, ibuprofen, naproxen) and COX-2 selective NSAIDs, which are referred to as "coxibs", such as parecoxib, celecoxib, etoricoxib, all act by inhibiting the prostaglandin synthesis in the peripheral tissues, nerves, and in the central nervous system (CNS) (70). These are integral components of the multimodal postoperative analgesia with an opioid-sparing effect of approximately 40% (71). Perttunen et al. (72) demonstrated that after thoracotomy, diclofenac infusion decreases the need for an opioid by 75%. However, non-selective NSAIDs have many adverse effects, such as irritating the GI tract and impairing platelet aggregation, causing postsurgical bleeding. Even though the coxibs are safer in terms of these risks, they have been reported to increase the risk of thromboembolic complications after coronary artery bypass grafting (CABG) in those patients with atherosclerotic disease (73), but not after non-cardiac surgery (74, 75). Mainly due to these cardiovascular risks, valdecoxib and rofecoxib were globally withdrawn in 2005. In contrast, valdecoxib and its prodrug, parecoxib, produce effective postoperative analgesia and decrease opioid requirement by 30-40% (76). Diclofenac and valdecoxib also have been shown to cross the blood-brain barrier and they could prevent central sensitization and even chronic pain (77-79). However, no firm evidence has thus far been reported on the overall benefits of coxibs over non-selective NSAIDs with postoperative analgesia (80).

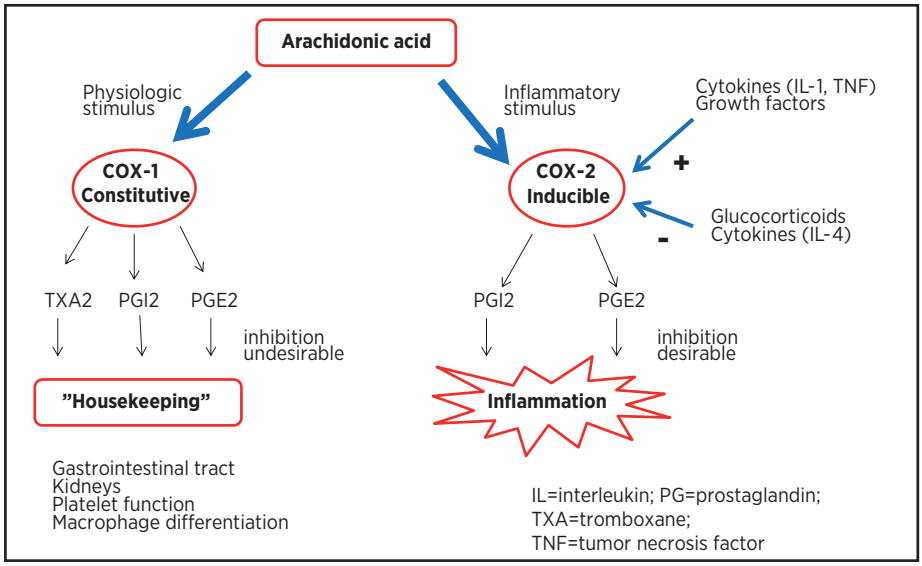


Figure 2. The function of COX-1 and COX-2 enzymes. Adapted from Brzozowski T et al, J Physiol Pharmacol 2005; 56:33-55.

2.2.3. PARACETAMOL

2.2.3.1. The mechanism of action of paracetamol

Paracetamol is a weak analgesic because to achieve at least 50% pain relief after surgery, the NNT (number-needed-to-treat) for paracetamol 1 g perorally, is 3.6 (81). According to the meta-analysis by Remy et al. (82), paracetamol combined with IV-PCA morphine induced a 20% morphine-sparing effect without reducing the adverse effects related to morphine. Paracetamol also crosses the blood-brain barrier (83), and its analgesic action may be mediated via the central anti-inflammatory pathways. Moreover, the earlier theory on the inhibition of the cyclo-oxygenase-3 enzyme (COX-3) has been abandoned (84). Paracetamol may also act in the central nervous system as a selective COX-2 inhibitor, where the concentration of tissue peroxides is low, contrasting the sites of inflammation (85, 86). The indirect activation of cannabinoid (CB1) receptors also explains part of the analgesic action of paracetamol, as well as some of its subjective effects, such as euphoria, relaxation, and the feeling of tranquility (87-89).

2.2.3.2. Possible interaction of paracetamol and 5HT3-antagonists

Pelissier et al. (27) and Alloui et al. (28) have demonstrated in studies using rats that intrathecal tropisetron, a specific 5HT3-antagonist, completely abolishes the antinociceptive action of paracetamol. Because paracetamol does not bind to 5HT receptors *in vitro,* the serotonergic action would be indirect (89). However, other 5HT3-antagonists (ondansetron, granisetron) administered intrathecally did not attenuate the antinociceptive effect of paracetamol, suggesting that the antagonistic effect of tropisetron would be mediated through a specific receptor that is sensitive to tropisetron (89, 90). Recently, these results have been questioned after controversial findings have been published concerning the ability of ondansetron to attenuate the analgesic action of paracetamol in mice (91, 92).

Two studies on healthy volunteers, conducted by Pickering et al. (29, 30), suggested that paracetamol reinforces the descending serotonergic pathways that are involved in pain inhibition in humans. Pain was measured by an electrical median nerve stimulation (PainMatcher®) (29) and mechanical pain threshold before and after a cold pressor test (CPT) (30). The result was that both tropisetron and granisetron completely blocked the analgesic action of paracetamol 1g perorally due to a pharmacodynamic interaction. Yet clinical studies have questioned these preclinical findings. In some studies, the analgesic action of paracetamol was not affected by ondansetron after a hysterectomy (93), or by tropisetron after ear surgery (94). Furthermore, Bandschapp et al. (95) observed that both paracetamol and tropisetron had a weak analgesic effect in the intracutaneous electrical

stimulation test when administered alone to healthy volunteers without any effect on hyperalgesia or allodynia. However, when simultaneously administered, the analgesic action of both drugs disappeared. Thus as the importance of the possible interaction of paracetamol and the 5HT3-antagonists cannot be ignored because paracetamol is commonly used to manage postoperative and cancer-related pain, and as 5HT3-antagonists are simultaneously administered to manage postoperative and chemotherapy-induced nausea and vomiting.

2.2.4. EPIDURAL ANALGESIA

In epidural analgesia, opioids and/or local anaesthetics are continuously administered into the epidural space via an indwelling catheter. The common epidural local anaesthetics, ropivacaine 0,2 % and levobupivacaine 0,125 %, provided similar analgesia without a motor block when infused via thoracic epidural catheters during lung surgery (96). These concentrations of epidural local anaesthetics were equivalent to 0,125 % bupivacaine after hip surgery (97). The total dose of local anaesthetics infused was more important than their concentration or volume after thoracotomy (98) and lower abdominal surgery (99).

Of all the types of abdominal and thoracic surgeries, thoracic epidural analgesia (TEA) provides better postoperative pain relief than parenteral opioid administration – including IV-PCA (49, 100, 101). In comparison to systemic opioid administration, TEA resulted in significantly lower pain scores after abdominal aortic surgery in comparison with systemic opioid administration, a reduced duration in intubation and mechanical ventilation, and lower rates of cardiovascular complications, including myocardial infarction, acute respiratory failure, gastrointestinal complications and renal insufficiency (102). According to Ballantyne et al. (103), due to its superior efficacy especially in relieving dynamic pain, TEA prevents postoperative pulmonary morbidity after lung surgery. Furthermore, combining low concentrations of local anaesthetics and opioids (for example, lipophilic fentanyl) has been shown to provide superior pain relief when compared to either of the drugs alone (68, 69, 104).

TEA is, however, an invasive method that cannot be used in every patient due to the increasing use of long-acting anti-thrombotic prophylaxis. In a Finnish study all claims attributed to central neuraxial blocks and handled by the Patient Insurance Centre (PIC) during 2000-2009 were analyzed. Fatalities during perioperative epidural pain management occurred in 1:62 000 due to errors in medication, unintended total spinal anaesthesia, infection or consequences of nerve damage, and the incidence of epidural haematoma was 1:26 400 (105). Much higher incidence of epidural haematomas (1:10 300) was found in Sweden during 1990-1999, and the risk was up to 1:3 600 in elderly females undergoing knee arthroplasty (106). In United States the incidence was 1:4 330 – 1:22 189 (107). Due to these serious

risks, the Acute Pain Service (APS; see chapter 2.4.) has a crucial role in observing the patients treated with invasive analgesic techniques, such as epidural analgesia and IV-PCA opioids (108-110).

2.2.5. ADJUVANT DRUGS

Adjuvant analgesics are medications that are not primarily designed to control pain, but can be used for this purpose. Examples of these drugs are gabapentinoids, glucocorticoids and NMDA-receptor antagonists.

2.2.5.1. Gabapentinoids

Gabapentin is an antiepileptic drug that has been extensively used to treat diabetic polyneuropathy, postherpetic neuralgia, and neuropathic pain in general. The mechanism of action of gabapentin and its successor, pregabalin, has been investigated for chronic pain. This mechanism is mediated by selectively binding to the α2δ subunits of the presynaptic voltage-gated calcium channels, which are upregulated in the dorsal ganglia and in the spinal cord after surgical trauma (Figure 3). Gabapentinoids may produce antinociception by inhibiting calcium influx via these channels, and subsequently by inhibiting the release of excitatory neurotransmitters from the primary afferent nerve fibers in the pain pathway. The α2δ subunit is also a receptor for the proteins that promote synapse formation, called thrombospondins. The disruption of this synaptogenesis in central nervous system by the gabapentinoids may contribute to their analgesic effects. Gabapentinoids also inhibit glutamate release, decrease the activity of NMDA-receptors, inhibit voltage-gated sodium channels, and enhance the action of voltage-gated potassium channels. Additionally, the amplitude of a tonic inhibitory GABAergic conductance may be increased by the prolonged use of gabapentinoids. While both drugs lack hepatic metabolism and have known pharmacodynamic interactions, pregabalin has a more favourable pharmacokinetic profile than gabapentin (16-21).

In central sensitization, the excitability of neurons within the central nervous system is increased so that normal inputs begin to produce abnormal responses, which may occur in association with surgery that causes severe acute pain. Gabapentinoids have antiallodynic and antihyperalgesic properties that reduce the hyperexcitability as well as the central sensitization of the dorsal horn neurons. Gabapentinoids may also reduce opioid tolerance, and they have anxiolytic effects (111, 112).

Gabapentinoids have been widely tested in experimental pain models. Whereas the subjective pain ratings were unaffected by gabapentin in the heat pain and

the pinprick skin stimulation tests, the studies conducted on functional magnetic resonance imaging (fMRI) detected activation in the bilateral insula. However, the cold pressor test (CPT) was insensitive to gabapentin. Gabapentin has also displayed some analgesic effect against hyperalgesia and allodynia after cutaneous capsaicin stimulation, and the modulation of the cerebral response could be clearer for neuropathic pain than for acute pain. In addition, the relation between the dose and effect of gabapentin has been reported to be nonlinear (113). The allodynia and hyperalgesia that arose from continuous electrical stimulation were reduced after multiple doses of pregabalin, whereas temporal summation has not been determined to be attenuated. In other words, the results from experimental tests with gabapentinoids have been somewhat conflicting (113, 114).

In recent years, gabapentinoids have been introduced as adjuvants into the multimodal management of acute postoperative pain. A single preoperative dose of gabapentin has been suggested to reduce pain intensity, opioid consumption and opioid-related adverse effects for the first 24 h (115-120), but a low dose of gabapentin (250 mg) for the treatment of established postoperative pain was determined to be of limited clinical value (121). An optimal dose of pre-emptive gabapentin was then evaluated for administration before back surgery, and a large single dose of 22 mg/kg was found to be needed for analgesic efficacy (122). However, the focus of research has recently shifted to the perioperative use of pregabalin, which has been shown to produce a dose-related reduction in postoperative opioid consumption (123-125). Whereas the administration of 225-300 mg/day of pregabalin during a short perioperative period provided additional analgesia, it also created some adverse effects, such as dizziness and visual disturbances (123). In a Cochrane review, Moore et al. (126) detected no clear evidence of the beneficial effects of pregabalin in acute postsurgical pain, and the efficacy of pregabalin in acute postoperative pain was suggested to be somewhat dependent on the type of the surgery (127, 128).

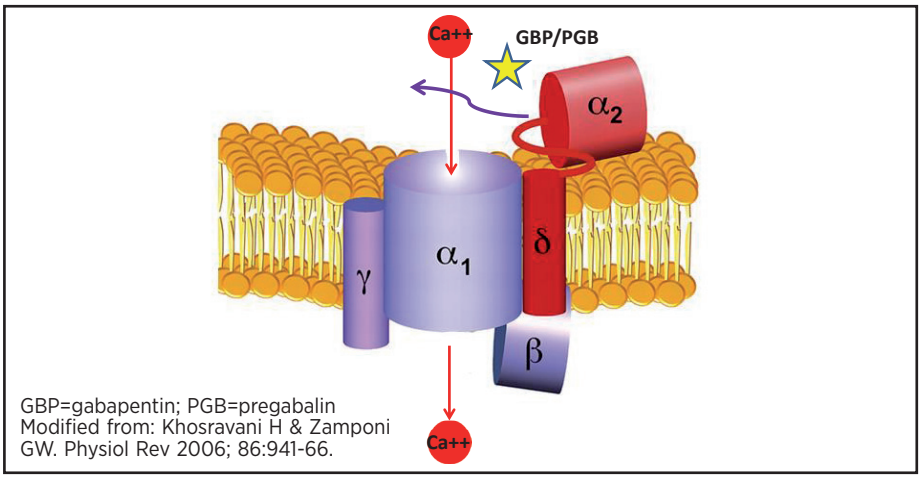


Figure 3. The binding site of gabapentinoids.

2.2.5.2. Glucocorticoids

A popular subject of research concerning the prevention of postoperative nausea and vomiting, and to a lesser extent, postoperative analgesia, has been systemic glucocorticoids. A safe and effective method that has been proven to reduce the pain from orthopaedic and breast surgery (129, 130) is methylprednisolone IV. One strong anti-inflammatory glucocorticoid with antinociceptive effects is dexamethasone. The effect of this glucocorticoid is to inhibit glial activation, sympathetic sprouting, the production of prostaglandins, bradykinin, leukotriens, TNF-α and other mediators of inflammatory hyperalgesia and central sensitization, including the systemic acute-phase response and the C-reactive protein (CRP) levels (22-26). Glucocorticoids also inhibit the synthesis of COX-2 in both the peripheral tissues and the central nervous system (131). The systemic analgesic effect of glucocorticoids has also been demonstrated after dental, anorectal and lumbar disc surgery, tonsillectomy and LCC, and they may reduce postoperative fatigue and PONV (132-136). Doses as high as methylprednisolone 30 mg/kg and dexamethasone 40-80 mg IV have been proven to be safe (134, 135, 137). The advantages of the preoperative administration of an intermediate dose of dexamethasone (0.1-0.2 mg/kg IV) is that it reduces postoperative pain and opioid consumption after various surgical procedures without any major adverse effects, apart from minor hyperglycemia at 24 h (138, 139).

The activation of the metabolic response to surgery occurs immediately after the incision. The onset of the biologic action of glucocorticoids takes one to two hours by changing the protein-synthesis by gene transcription. Thus, the optimal timing of dexamethasone would be one to two hours prior to surgery (140). However, glucocorticoids may also have rapid non-genomic effects by acting on the membrane receptors and could also therefore be useful also after surgery (141).

2.2.5.3. NMDA-receptor antagonists

Ketamine is an inexpensive drug that acts as a non-competitive antagonist of the NMDA-receptor in sub-anaesthetic doses, although it also binds to many other sites in the peripheral and central nervous system. At these doses, ketamine serves as an agent that is antihyperalgesic and antiallodynic by inhibiting the TNF-α and IL-6 gene expressions that result in subsequent anti-proinflammatory effects (142). Consequently, ketamine may be used as an adjuvant in the treatment of pain that is associated with central sensitization such as in severe acute pain, neuropathic pain and opioid-resistant pain (143). Bell et al. (144) reported that low-dose ketamine (up to 30 mg/24h) is effective in reducing morphine requirements in the first 24 hours after surgery, and ketamine also reduces PONV without having clinically relevant adverse effects of its own. Additionally, a 0.5 mg/kg IV bolus + 0.25 mg/

kg/h (4 μg/kg/min) infusion during general anaesthesia has been shown to provide long-term analgesia up to 6 months (145). Recently, in treating acute pain after thoracotomy, ketamine has also been shown to be a beneficial part of multimodal analgesia (146-150), but negative results have also been published (151).

It is important to note that the available literature on dextromethorphan for the treatment of postoperative pain is heterogenous. Controlled trials demonstrate that dextromethorphan does not reduce postoperative pain to a clinically significant extent, even though the time to the first analgesic request may be prolonged and a decrease in opioid consumption was also observed in the majority of the studies where the drug was administered parenterally (152). Hence, the role of dextromethorphan in postoperative pain management is still unclear.

2.3. PROCEDURE-SPECIFIC APPROACHES TO POSTOPERATIVE PAIN MANAGEMENT

The different types of surgical procedures (for example, orthopaedic, abdominal, thoracic and laparoscopic) each entail unique characteristics of postoperative pain and adverse clinical consequences, such as immobilization, ileus, urinary retention and the impairment of pulmonary function. As a consequence, analgesic techniques need to be targeted specifically for the procedure. For example, after major abdominal and thoracic surgery, continuous epidural analgesia is beneficial in reducing dynamic pain and ileus. Nonetheless, epidural analgesia is an invasive method with potential risks and it is not appropriate, for example, for day surgery, for some procedures with lower abdominal incisions and for laparoscopies. Peripheral nerve blocks and local infiltration analgesia (LIA) are increasingly used after orthopaedic surgery instead of epidural analgesia. In addition, analgesic drugs may have different side-effect profiles of analgesic drugs that depend on the type of surgery, such as conventional non-specific NSAIDs (not the coxibs) that create a risk of bleeding after tonsillectomy, hip and knee prosthesis operations, as well as after plastic and intracranial surgery (35).

2.3.1. THORACOTOMY

A perfect example of a major multifactorial postoperative pain is the acute pain that occurs after thoracic surgery. Acute post-thoracotomy pain is a combination of nociceptive, visceral and neuropathic pain that is evoked by breathing and coughing. The origin of the pain is due to incisional pain, the stretching of thorax, a resection or fracture of ribs, a dislocation of costovertebral joints, an injury to the intercostal nerves, the shoulder pain from a stretching position, and the visceral pain from the

irritation of the pleura by thick chest drains (153, Figure 4). If poorly treated, the risk of pulmonary complications and chronic pain increases (10, 103).

Compared to the IV opioids, thoracic epidural analgesia (TEA) provides superior analgesia compared to IV-PCA opioids, especially for dynamic pain (154-159). Enabling patients to cough properly, TEA is reported to prevent postoperative pulmonary morbidity after lung surgery (103, 160-163). In addition, the short-term quality of life postoperatively may be better with TEA than IV-PCA opioids due to better mobility, less sedation, improved compliance with physiotherapy, and more effective analgesia (164).

TEA is an invasive method that can cause serious adverse effects. Technical failures are also common (156, 165), and epidural haematomas, abscesses and other neurological complications have to be taken into account (see Epidural analgesia 2.2.4.). Hence, alternative analgesic methods to TEA are still needed in preventing acute and persistent post-thoracotomy pain.

An alternative to TEA is the paravertebral nerve block (PVB) with a bolus of a local anaesthetic preoperatively or at the end of surgery, which is followed by a continuous infusion via a catheter. Recent data confirms that PVB is comparable to TEA in controlling acute pain after thoracotomy, and that PVB has less haemodynamic adverse effects and a lower risk for neurological sequelae (166-168). In a situation

Photo by Dr Eija Nilsson

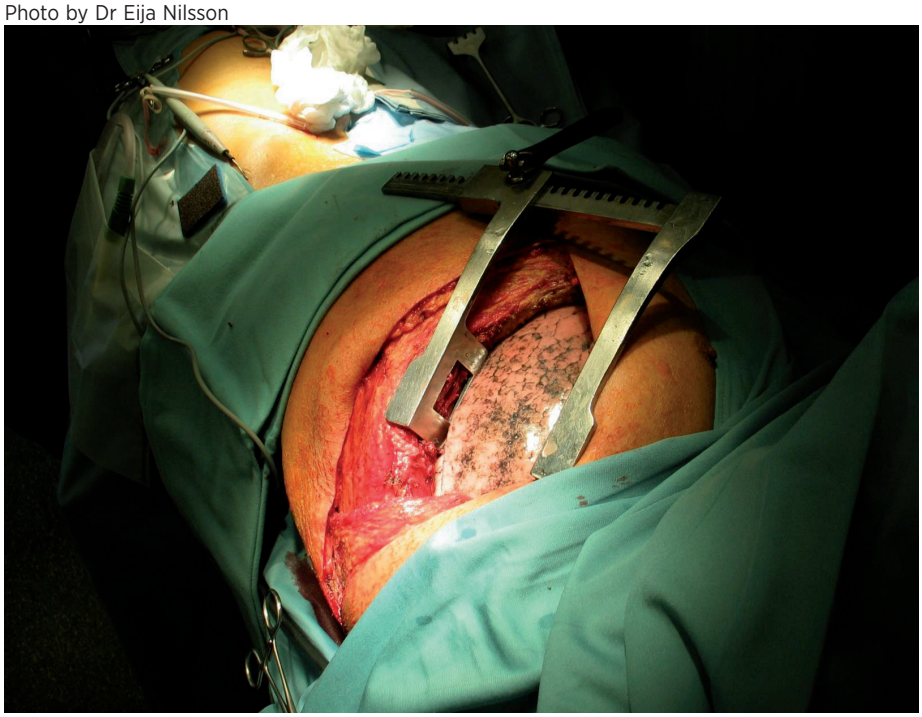


Figure 4. Origin of post-thoracotomy pain.

where neither TEA nor PVB is possible, it is recommended to use intercostal nerve blocks with local anaesthetics or to use IV-PCA with strong opioids. Furthermore, an integral part of a multimodal analgesic regimen in managing acute post-thoracotomy pain, if not contraindicated, is non-selective NSAIDs/ coxibs or paracetamol, which are enhanced later with weak opioids when the pain intensity has decreased to less than moderate (169).

2.3.2. LAPAROSCOPIC CHOLECYSTECTOMY

A good example of day surgery that involves moderate pain intensity (visual analogue scale, VAS 4-6/10) and sources of pain that are multifactorial is laparoscopic cholecystectomy (LCC). The somatic pain component is superficial incisional pain, and the visceral component is deep intra-abdominal pain caused by intraperitoneally insufflated carbon dioxide (CO_2) and bile spillage, causing chemical peritonitis. In addition, shoulder pain is referred visceral pain caused by CO_2 entrapped between the liver and the right hemidiaphragm, leading to irritation and stretching of the peritoneum. Also use of diathermy in the liver bed produces a systemic inflammatory response and hyperalgesic pain (170). The most common reasons for delaying a patient's discharge home are poorly controlled pain and PONV (2). Therefore, it is important to find a multimodal pain treatment, and a suitable PONV-preventing anaesthetic technique with infusions of propofol and remifentanil is also needed to hasten both the emergence from anaesthesia and postoperative recovery (2, 171).

2.4. ACUTE PAIN SERVICE

The use of invasive pain management techniques, such as epidural and IV-PCA, require close observation of the patients in the surgical ward. In a recent RCT, Lee et al. (109) compared an APS led by an anaesthesiologist to conventional pain treatment after major surgery. They demonstrated that the proportion of patients with highly effective pain management was higher in the APS group than in the control group, but with extra costs. However, a nurse-based model would further reduce costs, still maintaining the safety of pain management. APS has also a crucial role in recognizing those patients who are at risk of severe acute and chronic postoperative pain, and their educational programmes support nurses and doctors involved in pain management after surgery. Therefore, this kind of organization for the management of postoperative pain is strongly recommended worldwide (108, 110).

2.5. CHRONIC PAIN AFTER SURGERY

2.5.1. MECHANISMS AND PREDICTIVE FACTORS FOR CHRONIC POSTSURGICAL PAIN

Many common operations involve acute postoperative pain that is sometimes followed by persistent pain. These operations are, for example, breast and thoracic surgery, groin hernia repair, leg amputation, and coronary artery bypass surgery (Table 3). Acute pain may also become persistent through some pathophysiological processes after tissue or nerve injury occurs. An example of these injuries is the inflammation that can occur at the site of tissue damage with a barrage of afferent nociceptor activity that produces changes in the peripheral nerves, the spinal cord, the higher central pathways (central sensitization) and in the sympathetic nervous system (172-174). The mechanical hypersensitivity in the uninjured tissue area that surrounds the wound (secondary hyperalgesia) indicates central sensitization after surgery, and the extent of this correlates with the risk for chronic postsurgical pain, and this has been shown to occur after major abdominal surgery (175). Moreover, after limb amputation, the reorganization or remapping of the somatosensory cortex and of the other cortical structures may contribute to the development of phantom limb pain (176).

A number of risk factors for the development of chronic postsurgery pain have been identified. The following factors may be associated with an increased likelihood of persistent pain after surgery: severity of preoperative pain, nerve injury during and after the operation, persistent inflammatory process, genetic susceptibility, severity of early postoperative pain and psychosocial factors (4, 5, 174, 177-181, Table 4). In addition, a patient's immune response may also be involved in the transition of acute postsurgical pain to chronic pain. This has been demonstrated with patients after lateral thoracotomy when chronic postsurgical pain was decreased in lung transplanted patients who were treated with immunosuppressive therapy in comparison to patients who were operated on lung cancer (182). Another relevant factor may be the descending pathways of pain control, as patients with inefficient diffuse noxious inhibitory control (DNIC) – also referred to as "conditioned pain modulation (CPM)" - might have an increased risk of developing acute and chronic postsurgical pain (183, 184). It is important to notice that the intensity of acute postoperative pain correlates with the risk of persistent pain after surgery. Consequently, aggressive early therapy for acute pain could be a mainstay to prevent acute pain from converting into a chronic state. However, the transition from acute pain to chronic postsurgical pain is a dynamic process that evolves over time. As a consequence, assessing outcomes at a single follow-up after surgery does not provide information on whether the factors involved in the transition to chronic pain differ from those involved in the maintenance of already established chronic pain disability (180).

Table 3. Incidence of chronic pain after surgery (3-12 months postoperatively). Adapted from Kehlet et al. (4), Macrae (5) and Lavand'homme (7).

Type of operation	Incidence of chronic pain (%)	Estimated incidence of chronic severe (disabling) pain (NRS>5/10) (%)
Limb amputation	30–85	5–10
Thoracotomy	5-65	10
Mastectomy	11-57	5-10
Major abdominal surgery	7-14	n.a.
Craniotomy	7-29	n.a.
Knee arthroplasty	13	n.a.
Hip arthroplasty	12	n.a.
Cesarean section	4-10	4
Inguinal hernia	5-63	2-4
Coronary bypass	30-50	5-10
Cholecystectomy	3-50	n.a.
Vasectomy	0-37	n.a.
Dental surgery	5-13	n.a.

NRS=numeric rating scale (0-10). n.a.=not available. All numbers are based on both retrospective and prospective studies.

Table 4. Risk factors for chronic postsurgical pain. Adapted from Kehlet et al. (4), Macrae (5) and Andersen & Kehlet (179).

Preoperative factors	Preoperative pain, moderate to severe, lasting more than 1 month in the surgical area
	Preoperative chronic pain in other locations
	Repeat surgery (e.g. cancer recurrence)
	Psychologic vulnerability (e.g. catastrophising, anxiety)
	Female gender
	Obesity (risk to nerve damage during surgery)
	Younger age (adults)
	Workers' compensation
	Genetic predisposition
	Inefficient DNIC, diffuse noxious inhibitory control (=CPM, conditioned pain modulation)

Intraoperative factors	Surgical approach with risk of nerve damage
	Tissue ischaemia
	Proinflammatory state
Postoperative factors	Acute pain (moderate to severe), hyperalgesia
	Radiation therapy to the surgical area
	Neurotoxic chemotherapy
	Sensory disturbances after surgery
	Surgical complications (infection, seroma, hematoma)
	Repeat surgery
	Psychological vulnerability, anxiety

2.5.2. CHRONIC POST-THORACOTOMY PAIN

The International Association for the Study of Pain (IASP) defines post-thoracotomy pain syndrome (PTPS) or chronic post-thoracotomy pain as, "pain that recurs or persists along thoracotomy incision at least two months following the surgical procedure". Generally, this entails a burning and stabbing pain with dysaesthesia and displays many features of neuropathic pain in nearly half of the patients experiencing pain (10, 185). The risk of PTPS may be predicted by preoperative pain, female gender, younger age, psychological factors, severe acute postoperative pain, high consumption of analgesics during the first postoperative week, and the type of surgery and complications (11, 12, 186-188). Even muscle-sparing incisions seem to have no advantage over posterolateral incisions (189). However, intraoperative intercostal nerve damage during thoracotomy is not necessarily associated with PTPS (190, 191). Chronic post-thoracotomy pain was commonly diagnosed by surgeons during the Second World War in those soldiers who had undergone a thoracotomy for chest trauma; this was called "chronic intercostal pain". Unfortunately, very little has changed since then in terms of the numbers of patients with PTPS.

During the past decade, due to it being a minimally invasive procedure, video-assisted thoracic surgery (VATS) has partially replaced open thoracotomy for lung surgery. This is because rib retractors are not needed in the thoracoscopic approach and the integrity of the chest cage is preserved with less trauma to the patient's intercostal nerves and ribs. Therefore, the acute pain that occurs after VATS is considerably milder than after a thoracotomy (192, 193). However, VATS also carries a risk of nerve damage and a development of persistent pain in 5-47% of the patients, yet less risk is involved than after open surgery (188, 194, 195).

Some evidence suggests that TEA could prevent central sensitization and long-term post-thoracotomy pain (155, 186), but this evidence is still controversial.

For example, the "pre-emptive analgesia" attempts to reduce post-injury pain hypersensitivity by starting the treatment before the surgical procedure rather than afterwards. However, this concept is controversial, and it would be more relevant to talk in terms of "preventive analgesia" so that the persistence of the analgesic effect after the treatment has ceased. Preventive analgesia is based on the assumption that the only way to prevent central sensitization is to completely block any pain and afferent signals. This includes a complete humoral blockade of the circulating pro-inflammatory cytokines from the surgical wound, and this occurs from the time of the incision until the wound heals (174). Sentürk et al. (196) demonstrated that initiating epidural analgesia prior to a thoracotomy incision and continuing postoperatively results in significantly less pain in the acute phase and six months later compared to IV-PCA opioids or TEA initiated after surgery. In a meta-analysis, Bong et al. (197) found that pre-emptive TEA appeared to reduce the severity of acute pain without any effect on the incidence of persistent pain.

The role of opioid-induced hyperalgesia induced by high-dose remifentanil cannot be ignored. High-dose remifentanil without epidural analgesia during surgery was associated with a large allodynic area around the thoracotomy wound and a higher incidence of chronic pain, compared with perioperative low-dose remifentanil and TEA (198). Overall, it seems that thoracic epidural anaesthesia may be effective in reducing the post-thoracotomy pain syndrome; however, the timing of the initiation of the TEA may not be significant (14).

Some evidence suggests that PVB may decrease the incidence of chronic pain after breast surgery which resembles PTPS due to the predominance of neuropathic features (199, 200). However, the role of paravertebral blocks in preventing PTPS has not been investigated.

Low-dose ketamine appears to be useful in decreasing acute post-thoracotomy pain as part of multimodal analgesia (see Chapter 2.2.5.3.). Unfortunately, there is no evidence of a more sustained benefit in preventing PTPS (201, 202). Senard et al. (203) published promising results on the first randomized controlled trial (RCT) involving COX-2 inhibitors (celecoxib) with TEA for acute post-thoracotomy pain. Nevertheless, there is no literature on the effect of selective or non-selective NSAIDs on PTPS. Whereas epidural clonidine, even as a sole agent, has decreased acute post-thoracotomy pain (204), no evidence has been found on its long-term effects. Gabapentinoids as antihyperalgesic drugs would be an attractive choice for the management of acute and prevention of chronic post-thoracotomy pain. The results are, however, controversial in acute pain (205, 206), and there is currently no literature on the use of gabapentinoids to prevent PTPS.

3. AIMS OF THE STUDY

The main purpose of the present work was to investigate the intensity of acute postoperative pain and incidence of chronic pain after surgery. In addition, an analysis will be presented of the possibilities for improving postoperative pain management with multimodal analgesia and in preventing persistent pain after surgery.

The specific aims were:

1. To survey the incidence of persistent post-thoracotomy pain (Studies I and IV).

2. To investigate whether the controlled pain management protocol extended also to the sub-acute postoperative phase would result in less acute and persistent post-thoracotomy pain in comparison to standard "as usual" pain management (Study IV).

3. To evaluate if IV-PCA morphine combined with NSAIDs (non-selective versus COX-2 selective), and thoracic epidural analgesia are safe and effective after thoracotomy (Study IV).

4. To assess the efficacy of paracetamol or pare/valdecoxib with or without dexamethasone following day-case laparoscopic cholecystectomy (Study II).

5. To assess the quality of pain relief after thoracic surgery and laparoscopic cholecystectomy at home during the first week after a patient is discharged (Studies I, II, IV)

6. To evaluate RCTs that examine the analgesic efficacy, adverse effects, and the clinical value of gabapentinoids in postoperative pain (Study III, a systematic review).

7. To test whether tropisetron, a 5HT3-antagonist, affects the analgesic effect of paracetamol in three different models of acute pain in healthy volunteers (Study V).

4. MATERIAL AND METHODS

Clinical studies I and IV included a total of 252 thoracotomy patients, and in study II 160 day-case LCC patients were involved. Study III was a systematic review about perioperative gabapentinoids, and Study V was an experimental volunteer study to find out the interaction between paracetamol and tropisetron.

4.1. MATERIAL

4.1.1. PATIENTS (STUDIES I, II AND IV)

Studies I and IV included patients who were scheduled to undergo a thoracotomy for lung surgery, and these were performed at the Department of Thoracic Surgery in Meilahti Hospital, which is a part of the Helsinki University Central Hospital. The consecutive patients in Study I were enrolled between April 1999 and August 2000, and 111 patients in total were analyzed. Both elective and emergency patients were included. Study IV examined two different groups of thoracotomy patients: an intervention group (n=30) and a control group (n=111). The exclusion criteria in the intervention group were contraindications to any of the study drugs or an epidural catheter, significant liver, renal or cardiac disease, peptic ulcer, regular use of analgesics, re-thoracotomy, and the patient's inability to understand the use of PCA/patient controlled epidural analgesia (PCEA; 207). The patients were recruited between April 2004 and September 2008. The control group consisted of patients who were treated according to the current standard of care at the clinic.

Study II included 160 patients of the ASA physical status I-II who were scheduled for elective ambulatory laparoscopic cholecystectomy (LCC) between the years 2003 and 2006 at the the Day Surgery Unit of Maria Hospital, which is part of the Helsinki University Central Hospital. Other inclusion criteria of the patients were their age, that they are between 18 to 60 years and have a body mass index (BMI) between 17 and 31. The exclusion criteria included having an allergy to NSAIDs or sulphonamides, bronchial asthma, liver or renal disease, peptic ulcer, bleeding disorders and regularly using analgesics. One patient was excluded from the analyses owing to a reoperation due to bleeding.

4.1.2. STUDIES III AND V

Study III was a systematic review that evaluated 22 RCTs (a total of 1 909 patients) examining the analgesic efficacy, adverse effects, and the clinical value

of gabapentinoids (gabapentin and pregabalin) in postoperative pain. This review covered the literature from 1966 to September 2006. Study V consisted to 2 different studies (Study 1 and Study 2), that included 18 healthy male volunteers. Out of the 18 volunteers who participated in Study 1, 12 also participated in the second study. In Study 1/V, the mean age was 23 (SD 3) and the mean BMI was 23 (SD 3), and in Study 2, the mean age was 24 (SD 3) and the mean BMI was 24 (SD 3). The exclusion criteria included a contraindication to either of the study drugs, smoking more than nine cigarettes per day, excessive consumption of tea or coffee (more than four cups per day) or taking any medications during the two weeks preceding the study. The first study was conducted in July 2009 and the second study was conducted in October 2010.

4.2. ETHICAL ISSUES

Studies I, II, IV and V were approved by the Institutional Ethics Committee and Studies II, IV and V by the National Agency of Medicine (NAM). A written informed consent was obtained from all the patients and volunteers.

4.3. STUDY DESIGNS, PROTOCOLS AND INTERVENTIONS

4.3.1. STUDIES I, II AND IV

Study I is a prospective clinical follow-up study that enrolls all the consecutive patients (n=111) who underwent a thoracotomy between 1999 and 2000. This study was not randomized nor controlled, because the anaesthesiologist in charge selected the method of pain treatment. Thoracic epidural analgesia (TEA) was considered to be the standard treatment (n=89; for characteristics of TEA, see Study I/Table 2), and the alternatives were IV-PCA with oxycodone and an intrathoracic intercostal block with bupivacaine at the end of the surgery (n=18). Four patients had conventional pain treatment with intramuscular oxycodone. All patients were also administered oral NSAIDs or paracetamol regularly from POD 1, in addition to a weak opioid (tramadol or paracetamol with codeine) that was administered after discontinuing the TEA or IV-PCA. The patients were prescribed regular ibuprofen or paracetamol and tramadol for home and were given instructions on how to take the analgesics. The patients were also encouraged to phone the APS nurse when needed. All patients were interviewed on the phone using a structured questionnaire a week after their discharge, the interview was repeated three and six months after the thoracotomy through a mailed questionnaire (Appendix 1).

Study II is a prospective, randomized, double-blind clinical study that enrolled 160 elective, ambulatory LCC patients. All patients were given glycopyrrolate and tropisetron followed by a general anaesthesia that was induced by fentanyl, propofol and rocuronium. The anaesthesia was maintained with infusions of propofol and remifentanil, maintaining the bispectral index (BIS) at 40-50. Warm CO_2 insufflation was used and intra-abdominal pressure was maintained under 12 mmHg. At the end of the surgery, the incisions were infiltrated with levobupivacaine.

The patients were randomly divided into four study groups. The patients in Group 1 (n=40) were administered doses of 40 mg of parecoxib 40 mg IV intra-operatively followed by an oral dose of 40 mg x1 of valdecoxib for seven days, started in Phase 2 PACU. The patients in Group 2 (n=40) were given 1g of paracetamol IV, and the first dose was administered at the same time as for Group 1. An oral dose of 1g of paracetamol was continued four times per day for seven days. Patients in Group 3 (n=40) were administered parecoxib and valdecoxib similarly to those in Group 1, and were administered 10 mg of dexamethasone IV which was administered intraoperatively. Patients in Group 4 (n=40) were given paracetamol similarly to those in Group 2 and 10 mg of dexamethasone IV. The staff nurse who administered the study drugs was not otherwise involved in the study. The rescue medications in Phase 1 PACU were 0.05 mg/kg of oxycodone IV when the pain measured on a visual analogue scale (VAS) was >3, and 0.01 mg/kg of droperidol IV for PONV. During Phase 2 PACU, the patients were given 0.15 mg/kg of oxycodone orally when needed. The patients were supplied with the study drugs for 7 postoperative days and were instructed to take 40 mg of valdecoxib every morning or 1g of paracetamol 4 times per day as long as needed. All patients were interviewed by phone on the first postoperative morning, and they also filled in a structured questionnaire for seven postoperative days (Appendix 2). This follow-up part of the study was not blinded.

Study IV included a prospective, randomized and partially double-blind clinical study consisting of 30 elective study patients (intervention group), and another non-randomized group of 111 control patients (control group) who underwent a thoracotomy for lung surgery between 2004 and 2008. The patients in the intervention group were randomly divided into three groups: 1) diclofenac + IV-PCA (n=10), 2) parecoxib/ valdecoxib + IV-PCA (n=10), and 3) PCEA (n=10). All patients were premedicated with temazepam. The patients in Groups 1 and 2 received oral doses of 75 mg of diclofenac or 40 mg of valdecoxib, respectively. At wound closure, a 44-hour IV-infusion began of 150 mg/24h of diclofenac (Group 1) or 80 mg/24h of parecoxib (Group 2), and an intercostal nerve block with bupivacaine was performed. Patients were given an IV-PCA with morphine boluses 2-3 mg and a lock-out time of 5 to15 minutes in the PACU. From the second postoperative morning onwards, the patients in Group 1 were given oral diclofenac 75 mg x2, and the patients in Group 2 valdecoxib 40 mg x2 until discharge. The IV-PCA morphine

was discontinued after the removal of the pleural drains, and oral oxycodone was provided when needed. The patients in Group 3 received epidural catheters in the evening before their surgery. At that time, the catheters were also tested. The PCEA patients were administered IV 1g of paracetamol and an epidural loading dose of 1 ml/10 kg of bupivacaine 1.5 mg/ml with 6 μg/ml of fentanyl at the induction of anaesthesia. A continuous infusion began at 1 ml/10 kg/h with an option to take incremental doses of 3 ml with a 8-15 min lock-out time. The PCEA patients received IV 1g of paracetamol 4 x for the first 24 hours and 1 g x3 orally thereafter. PCEA was discontinued and paracetamol was replaced with ibuprofen and oral oxycodone after removal of the pleural drains, which is similarly to Groups 1 and 2. All patients were prescribed ibuprofen or paracetamol and tramadol for home after their discharge from hospital, and they were encouraged to contact the research nurse or the researchers when needed, which was the same procedure as in Study I. The extended controlled pain management protocol consisted of observation by APS seven days a week and prescription of weak opioids for home in addition to NSAIDs /paracetamol. Furthermore, the patients were carefully instructed how to use the analgesics at home, and they were contacted by phone one week after discharge, with a possibility to give further information and prescribe more analgesics if needed. The schedule of Study IV is shown in Figure 5.

The standardized anaesthesia consisted of an induction with glycopyrrolate, fentanyl, propofol and rocuronium, and maintained with sevoflurane in a mixture of oxygen and air. The depth of anaesthesia was monitored with the BIS. The thoracotomy was anterolateral, sparing the latissimus dorsi muscle, in 25 patients and posterolateral, sparing the serratus anterior muscle, in 5 patients.

The study was double-blinded for intervention Groups 1 and 2, and identical study medications were prepared by the hospital pharmacy. The hospital pharmacy also prepared the computer-generated randomization schedule.

The control group consisted of patients who did not meet the inclusion criteria for the study. The control group was included to determine whether persistent post-thoracotomy pain could be better minimized with an extended, strictly controlled pain management protocol than with current standard pain management in the clinic. These patients were treated during the same time period as the intervention patients. The standard care consisted of TEA with NSAIDs and/or paracetamol, followed by oral opioids with NSAIDs after TEA at the hospital and NSAIDs/ paracetamol at home. If TEA was contraindicated, the patients were provided with IV-PCA. Before the control group patients were discharged, they agreed to fill in the prospective follow-up questionnaire six months after the surgery. They also granted permission to data extraction from the perioperative period. The questionnaires used after six months were similar to the ones used for the intervention and control patients (Appendix 1). The questionnaires were mailed to 129 control patients, and the response rate was 86% (111 patients).

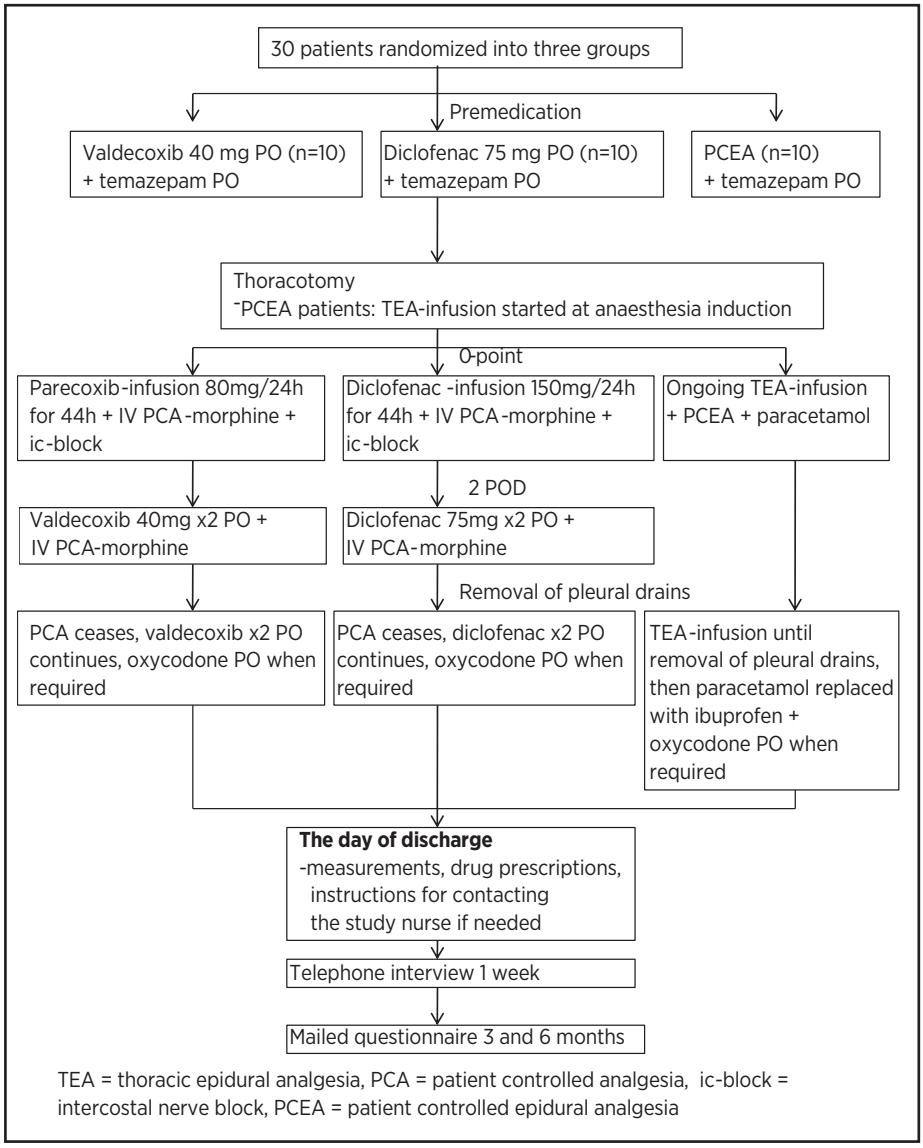


Figure 5. The schedule of Study IV.

4.3.2. STUDIES III AND V

Study III is a systematic review performed according to the standards described in "The Quality of Reporting of Meta-analyses" (QUOROM) statement (208). The databases of Medline (from 1966), PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL), were systematically searched for the terms "gabapentin or pregabalin or gabapentinoids" or "Lyrica or Neurontin" and "postoperative pain". Additional information on trials were inquired from the Pfizer Corporation, and the

reference lists of reports and reviews were checked. The last study that was included was published in September 2006. All randomized, placebo- or active-controlled, double-blind human trials were included if they had a minimum of ten patients in each study group as recommended by L'Abbe et al. (209). The interventions were a treatment with oral gabapentin or pregabalin in any dose during the perioperative period. A total of 22 trials of the perioperative administration of gabapentin or pregabalin for postoperative pain relief met the inclusion criteria.

Study V consists of 2 randomized, double-blind cross-over studies with 18 healthy male volunteers in each. The volunteers in Study 1 were tested twice with a period of one week between the test sessions. Heat tolerance was measured using a 30 x 30 mm contact thermode that was connected to a participant's right calf. First a measurement was taken of the temperature at which the volunteer reported moderate pain (4-6 on a numeric rating scale, NRS of 0-10) was measured by increasing the test temperature by 2 degrees at 6-second intervals from 32° to 48°C. This target temperature served in the following tests as the volunteer's individual heat stimulus, and the sensation was assessed on an NRS of 0-10. The cold pressor test (CPT) was performed by immersing a participant's right hand in cold water (+3°C) for five to ten minutes after the last heat stimulus, and the volunteer assessed the intensity and unpleasantness of the pain (0-10) every 15 seconds until he or she felt the need to withdraw his or her hand, continuing up to 90 seconds at the most. These testing procedures did not induce any tissue injury or inflammation.

After the baseline measurements the volunteers were administered 5 mg of tropisetron or saline IV in a randomized, double-blind manner, and 30 minutes later they received 2 g of paracetamol as an IV infusion. Pain measurements were then performed at 30, 60 and 120 minutes after paracetamol was administered. All volunteers were given both tropisetron and a placebo in a balanced random manner at a week's interval, repeating the test procedure 2 x 18 = 36 times, and the volunteers served as their own control.

In Study 2, the same 18 volunteers were contacted. Twelve of the volunteers participated in the second study and only six new volunteers were recruited. To determine pain and sensory in the participants, an electrical pain stimulus was induced by the Pain Matcher, which is a tool for pain autoevaluation that is based on the stimulation of the median nerve. The volunteers were instructed to place an electrode box located on the table between their first and second fingers of their dominant hand. Then, a constant stimulation by electric current (10 Hz, 10 mA) was provided that intensified the stimulus by successively increasing the pulse width from 0 to 450 μs in increments of 7.5 μs, up to a total of 90 steps. This electric current halted as soon as the volunteer released his grip, and the value reached (between 0 to 90 seconds) was saved in the memory of the device. After measuring the baseline pain and sensory, the volunteers were administered tropisetron or saline according to the same protocol as in Study 1. The measurements were subsequently repeated

20 minutes later, and after 30 minutes, 2 g of paracetamol was administered IV, which was followed by measurements at 30, 60 and 120 minutes after the paracetamol had been administered.

The study designs and interventions of all the studies are shown in Table 5, and the flow charts of the clinical studies (I, II and IV) are presented in Figure 6.

Table 5. Study designs and interventions

	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Participants	Elective thoracotomy patients (n=111)	Elective ambulatory LCC patients (n=159)	Surgical patients receiving gabapentinoids (n=1909)	Intervention group: elective thoracotomy patients (n=30); Control group: thoracotomy patients not eligible for the study (n=111)	Healthy male volunteers (n=18)
Study design	Prospective clinical follow-up study, open	Prospective, rando-mized, double-blind clinical study	Systematic review	Intervention: prospective, randomized, partially double-blind clinical study; Control: prospective clinical follow-up study, open	2 randomized, double-blind cross-over studies, volunteers
Intervention	Choice of the method of pain treatment by the anaesthetist in charge: TEA/ oxycodone-PCA/im oxycodone; ibuprofen/ paracetamol + tramadol for home	1) Pare/ valdexocib 2) Paracetamol 3) Pare/ valdecoxib + dexamethasone 4) Paracetamol + dexamethasone	Systematic literature search: controlled, double-blind human trials of perioperative gabapentinoids (n=22)	Intervention: 1) Diclofenac + IV-PCA 2) Pare/valdecoxib + IV-PCA 3) PCEA Ibuprofen/ paracetamol + tramadol for home Control: standard care	Experimental studies (paracetamol, tropisetron) with cold pressor test, contact heat and electrical stimulation
Collection of data	Hospital files, telephone interview 1 week after discharge, mailed questionnaire after 3 and 6 months	Data at OR, phase 1 and 2 PACU, telephone interview on POD 1, questionnaire for PODs 1-7	Literature search	Data at OR, PACU, surgical ward (Intervention patients: measurements by researchers; Control patients: hospital files); telephone interview 1 week after discharge and a mailed questionnaire after 3 and 6 months (intervention), a mailed questionnaire after 6 months (control)	Standardized measurements by researchers

LCC=laparoscopic cholecystectomy; TEA=thoracic epidural analgesia; PCA=patient controlled analgesia; PCEA=patient controlled epidural analgesia;
OR=operating room; PACU=postanaesthesia care unit; POD=postoperative day

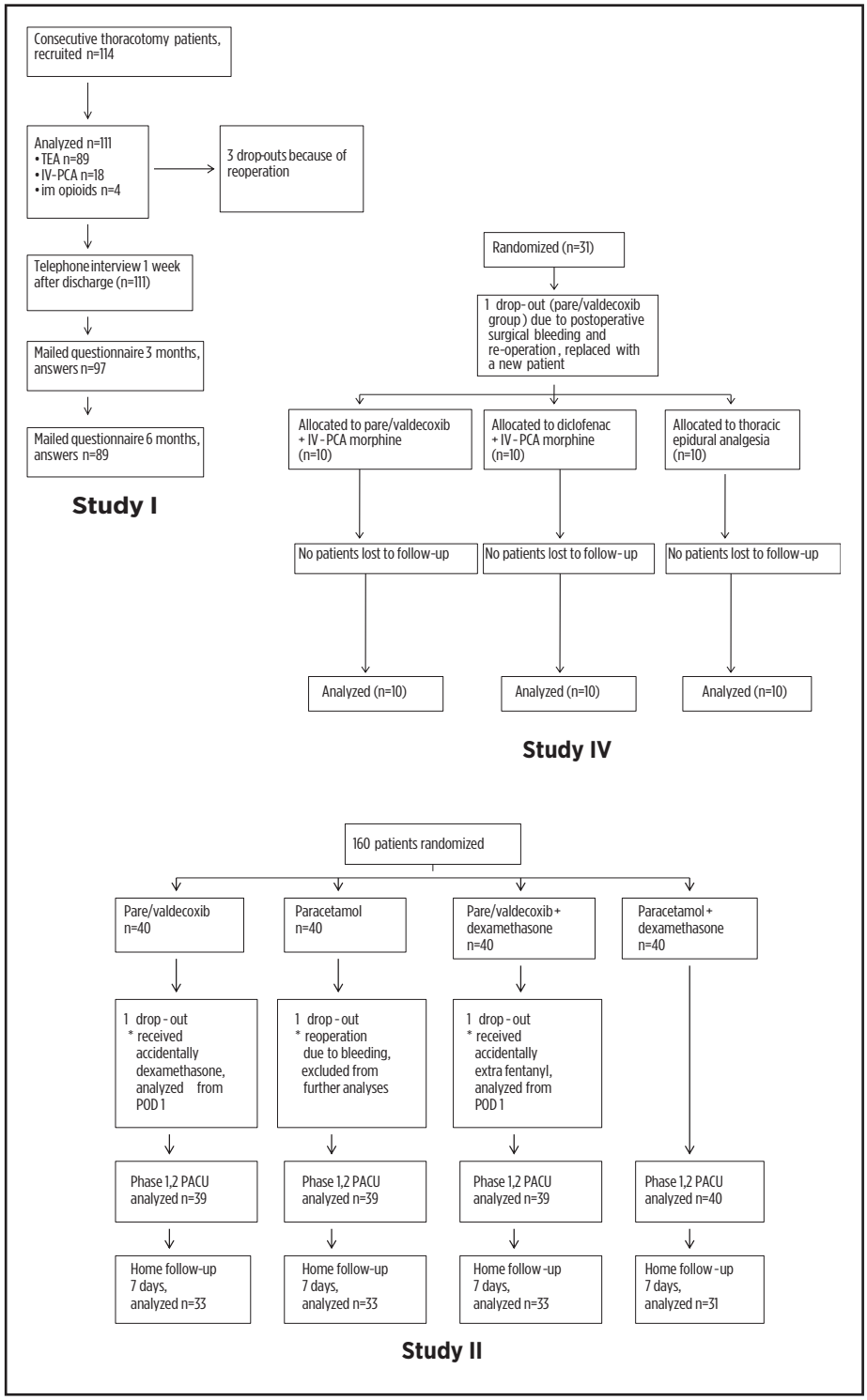


Figure 6. Flow charts of clinical Studies I, II and IV. POD=postoperative day, PACU= post-anaesthesia care unit

4.4. OUTCOME MEASURES

4.4.1. STUDIES I AND IV

In **Study I** (the first thoracotomy study), the primary outcome measure was the pain intensity while coughing on POD 1. The patients were measured for their pain intensity three times a day on the visual analogue scale (VAS) of 0-10cm (0 = no pain and 10 = worst imaginable pain) during rest and while coughing. The following factors were then recorded: the cumulative consumption of epidural fentanyl, the duration of pleural drainage and postoperative hospitalization, the duration of the TEA treatment, the patient satisfaction with the analgesia (scale "good-satisfactory-poor"), the adverse effects from TEA, and number of patients whose treatment was stopped prematurely (for example, due to catheter complications, adverse effects, etc.). During a telephone interview one week after discharge, the patients were requested to measure their pain during rest and while coughing by using a numeric rating scale (NRS). The patients were also asked about other issues, including the requirement of analgesics, the adequacy of the prescribed analgesics, their adverse effects and their difficulties in daily life including the disturbances in sleeping due to pain. Additionally, a record was made of the number of patients who needed further instructions on how to take their pain medication. A mailed questionnaire was subsequently sent three and six months after the thoracotomy. This questionnaire asked questions regarding the chronic pain that the patients experienced at rest and while coughing, the duration of their postoperative pain, their other symptoms related to their scar, such as numbness, activities that aggravated their pain, any difficulties they had in daily life and sleep, and their requirement of analgesics and other treatment for chronic pain. The patients were also asked to draw the localization and nature of their pain in a pain diagram (Appendix 1).

For **Study IV** (the second thoracotomy study), the primary outcome when comparing the intervention and control groups was the intensity of pain that occurred six months after a patient's surgery. When comparing the intervention groups (NSAID groups and PCEA group), the secondary outcomes were the pain intensity that the patients experienced while coughing during their first four postoperative days. This pain intensity was estimated on the VAS or NRS in the PACU. Pain intensity was also measured in terms of the pain intensity at rest and during physiotherapy, the consumption of PCA-morphine in Groups 1 and 2, the need for rescue medication, and the adverse effects (such as nausea, itching, sedation and subjective tiredness) as measured by the VAS. The study patients spent the first postoperative night in the PACU, and haemodynamic parameters and arterial blood-gases were analyzed. During this time a patient's pain was measured hourly for the first six hours after which the patients could sleep undisturbed. The next measurements were obtained by the study nurse in the morning, twice daily on the PODs 1-3, and then once per day until discharge. During the PODs 1-4, a

physiotherapist also evaluated pain at rest, while coughing, and after standing up. The success of physiotherapy was judged on a 0 to 10 scale (0 representing a failure of physiotherapy, and 10 indicating very successful physiotherapy).

Hyperalgesia was assessed by two methods. First, after the pleural drains were removed, the area of hyperalgesia was tested with a von Frey hair (210). The tested area of hyperalgesia was subsequently drawn, scanned and calculated by using pixels (area/cm^2). Then, "a coughing test" was performed, and the result was defined as the time needed for the cough-provoked pain intensity to return to baseline.

The study period lasted for the duration of the patient's hospital stay. Basic cardio-respiratory status was recorded twice daily for PODs 1-3, the s-creatinine and cystatine-C were followed before and after the operation, and daily urine output was measured during two PODs. The duration was also recorded of the hospitalization and pleural drainage, and any incidences of surgical complications were noted.

All patients in the intervention group were interviewed over the telephone a week after being discharged by using a structured questionnaire that was identical with that adopted in Study I. This questionnaire asked, for example, about the intensity of pain and the drugs taken. The patients' persistent pain was assessed three and six months later by administering a questionnaire that was mailed to the patients. This questionnaire was also identical to the one used in Study I (Appendix 1).

In the control group of Study IV, a record was made of the pain treatment method (IV-PCA or TEA), the acute pain intensity and consumption of analgesics, the adverse effects the patients experienced, and the success of pain management during their hospital stay. Six months after the operation, a questionnaire, which was similar to the one for the patients in the intervention group, was mailed to the control group.

4.4.2. STUDY II

In **Study II** (ambulatory LCC patients), the pain experienced at rest and in motion and the PONV were assessed in Phase 1 PACU using VAS (0-10 cm) every 20 minutes, as well as each time the patient requested oxycodone, indicating that the pain VAS>3. The time of the first dose of oxycodone was recorded. In Phase 2 PACU pain intensity and nausea were assessed at 30-min intervals, and whenever the patients requested oral oxycodone. The time of the patient's discharge from hospital was also recorded as well as the number of patients who had to stay unscheduled overnight. The patients were requested to fill in a questionnaire (Appendix 2) for seven PODs, evaluating their pain intensity (VAS) at rest and in motion as well as the localization of any pain three times per day, including any pain in the their right shoulder. They were also requested to document any additional medication they had taken and any adverse effects they had experienced. Additionally, the patients

were interviewed over the phone on the first postoperative morning before they started to fill in the questionnaire.

4.4.3. STUDIES III AND V

Study III is a systematic review on perioperative gabapentinoids. The following data were extracted in this study: publication details, patient population, number of patients, age, gender, surgical procedure, description of intervention, study design, duration and follow-up, intraoperative and postoperative analgesics, outcome measures, analgesic outcome results, withdrawals, and adverse effects. In addition, the sources of funding were checked to determine whether the trial was sponsored by the pharmaceutical industry and whether this was reported, as recommended by the CONSORT statement (211). The quality of the study (randomization/ allocation concealment, blinding measures, withdrawals and drop-outs) was evaluated using the Oxford Quality Scale (212), and the validity was examined using the Oxford Pain Validity Scale (213).

The main outcome measures were the pain scores, the total analgesic consumption for the first 24 hours, and the treatment-related adverse effects. The difference in pain intensity between the control and gabapentin groups was calculated by deducting the pain intensity in the treatment group from the value in the control group at different times. The number-needed-to-treat (NNT) was then calculated for the reduction of the adverse effects (nausea, vomiting, urinary retention) that were caused by gabapentin as compared to the placebo, and the number-needed-to-harm (NNH) was also calculated for the increase in sedation and dizziness during the 24-h follow-up after a single 1200 mg dose of gabapentin that was administered preoperatively (5 studies).

The first part of **Study V** (an experimental study with healthy volunteers) included the following primary outcome measures: the individual change in pain intensity (NRS 0-10) produced by the individually tested heat stimulus that provoked moderate pain at baseline, the individual change in cold pain intensity (NRS), cold pain tolerance (seconds) and cold pain unpleasantness (NRS). In the second part of the study, an electrical pain stimulus (Pain Matcher) was used. The primary outcome measures were the sensory threshold (time in seconds when the electrical pulses began to be detected), the pain threshold (when the pulses started to feel painful) and the moderate pain intensity (NRS 4-6/10). A literature search was conducted and an analysis was made for the human experimental pain models concerning the analgesic effects of paracetamol, and a review was made of all animal and human studies on the interactions of paracetamol and 5-HT3-antagonists.

4.5. STATISTICS

4.5.1. POWER ANALYSES

A power analysis was conducted in Studies II, IV and V. Study I was a prospective follow-up study without randomization, and Study III was a systematic review. In **Study II,** the sample size estimation was based on the hypothesis that a 25% reduction in opioid consumption by parecoxib and paracetamol would be clinically significant (71, 82), and the average pain intensity after LCC was extracted from the studies by Alponat et al. (214) and Aubrun et al. (215). After calculation, 32 patients per group were needed when the α error equalled 0.05 and the power equalled 90%. The sample size in **Study IV** was estimated for the NSAID + IV-PCA morphine versus the TEA with reference to Study I, in which the primary outcome measure was the pain intensity while coughing on POD 1. At least 23 patients per group were required when the α error equalled 0.05 and the power equalled 80% (a change in VAS of 2/10 with a SD of 2.3). In **Study V/part 1,** the sample size estimation was based on the assumption that the baseline level of pain induced by the heat stimulus is NRS 5 (SD 2), which is reduced to NRS 3 (SD 2) by paracetamol, and tropisetron abolishes its analgesic action completely (NRS 5, SD 2). Therefore, the adequate sample size would be 15.8 volunteers per group when the α error = 0.05 and the power = 80%. In **Study V/part 2,** it was assumed that the baseline level of pain induced by the intensifying electrical stimulus (tolerance in seconds) without medication is 25 s (SD 10). Paracetamol reduces that to 15 s (SD 10) and tropisetron completely abolishes the analgesic action of paracetamol (25 s, SD 10) (29, 30). Eighteen volunteers per study group were recruited in these two cross-over studies.

4.5.2. STATISTICAL METHODS

The descriptive data were presented as the mean ± SE (standard error, Study II) or the mean (SD, standard deviation) and the range, or as the actual numbers where appropriate. The $P<0.05$ was considered to be statistically significant in all studies. **Study I** compared the pain intensity on the day of discharge and the total cumulative consumption of epidural fentanyl using the Student's t-test (unpaired, two-tailed). In **Study II,** a statistical analysis was conducted of the demographic data and the single efficacy end points, and the one-way analysis of variance (ANOVA) was used. For the pair-wise comparisons, Bonferroni-corrected contrasts were used. The VAS scores for pain were treated as continuous parametric data and they were tested using ANOVA. The Kruskall-Wallis test was applied to the non-parametric data, such as the time until the first oxycodone dose and the amount of oxycodone needed. In addition, a Chi-square test was used to compare the number of patients that needed additional analgesics. These analyses were performed using NCSS for

Windows (version 2000). **Study IV** did not reach the intended sample size (see 5.1. Results), and consequently, primarily descriptive methods of analysis were adopted. Other analyses included the non-parametric methods, such as the Sign test and the Wilcoxon matched pair signed-rank test, the cross-tabulations with the chi-square test of independence and Fisher's exact test for statistical analyses. Parametric methods (Student's t-test and correlations) were adopted for the comparisons between the intervention patients and the control patients.

In **Study V/part 2**, the pain and sensory scores at each point in time were also expressed as a percentage of the individual score reported at baseline, which was calculated according to the following formula: Pain score = the pain detection threshold at the t(x) x 100/pain detection threshold before treatment (t0) (29). The sensory and moderate pain scores were then calculated equally. The variation in the pain measurements that were produced by tropisetron or by the placebo is a normally distributed continuous variable, and the differences between the groups were calculated using a repeated-measures ANOVA. To calculate the statistical analyses, a Prism4 for Macintosh (GraphPad Software Inc, La Jolla, CA) was utilized.

Study III concentrated on the quantitative analysis of the opioid consumption in the studies where a single, preoperative dose of gabapentin was administered, where the duration of the postoperative observation was at least 24 hours, and where the opioid consumption data were expressed as means, with an indication of variance. The consumption values of fentanyl and tramadol were scaled to arbitrary "morphine equivalent" units, using the conversion factors 100:1 and 10:1, respectively. The meta-analysis was calculated with the Comprehensive Meta-Analysis programme (version 2.2.027, Biostat, Englewood, NJ). The random effects model was selected to combine the materials that were based on the clinical heterogeneity that occurred across the individual studies, assuming a common among-study variance component across the subgroups. An analysis was then conducted using a metaregression to determine the possible dose-response on the opioid sparing effect of a single-dose of 300-1200 mg of gabapentin preoperatively for the first 24 hours. The pooled raw data method was subsequently used to calculate the NNT and NNH.

5. RESULTS

5.1. CHARACTERISTICS OF THE PATIENTS AND PROCEDURES IN STUDIES I, II AND IV

In **Study I,** three patients were excluded from the analysis due to their re-operation within a week after their first thoracotomy. Accordingly, the final number of patients included was 111. In **Study IV,** the intended sample size was not reached in the intervention group due to the global withdrawal of valdecoxib (73), and at the same time, thoracoscopic operations were replacing many open thoracotomies. Thus, the study was terminated after 30 patients had completed it, which was the size of one block in the randomization. NAM provided us a special permission to continue the study until 30 patients, presuming strict exclusion criteria concerning cardiovascular diseases. One patient from the valdecoxib group was withdrawn due to surgical bleeding and a re-operation and that patient was replaced with a new patient. In the intervention group, twenty-one patients (70%) had a malignant disease and nine patients had a benign disease (30%), and this difference was significant ($p<0.01$). Ninety-two of the 111 control group patients had a malignant disease (83%) and 19 patients had a benign disease (17%) ($p<0.01$). For details, see Table 6.

In **Study II,** 160 patients were recruited and 1 patient was excluded from the paracetamol group due to bleeding and re-operation. Out of the 159 patients who were initially scheduled for day-case LCC, 8 patients (5%) had to stay overnight in hospital. The reasons for this were postoperative pain (one patient), PONV (four patients), a surgeon's wish to observe the bleeding (two patients), and cardiac arrhythmias (one patient). For details, see Table 6.

The most common pre-surgery diagnoses in **Study I** were cardiovascular disease in 30% of the patients and respiratory disease (for example, bronchial asthma, COPD) in 14% of the patients. Other issues were musculoskeletal, endocrine (for example, hypothyreosis and diabetes), neurologic and psychiatric (including alcohol abuse). Fifty patients (45%) did not have a primary diagnosis. In the intervention group of **Study IV,** 13 patients (43%) had cardiovascular disease, 6 (20%) had respiratory disease, 3 (10%) had endocrine disease, and 1 (3%) had epilepsy. Eight (27%) patients had no pre-existing diagnosis. In the control group, 68% of the patients suffered from cardiovascular diseases, 35% from respiratory disease and 15% from endocrine disease; 20% had no pre-existing diagnosis. In the intervention study, a significant cardiac disease was a contraindication. In **Study II,** 13 patients (8%) had mild cardiovascular disease (hypertension or occasional arrhythmias), 7 (4%) had hypothyreosis and 25 patients (16%) had some other minor health

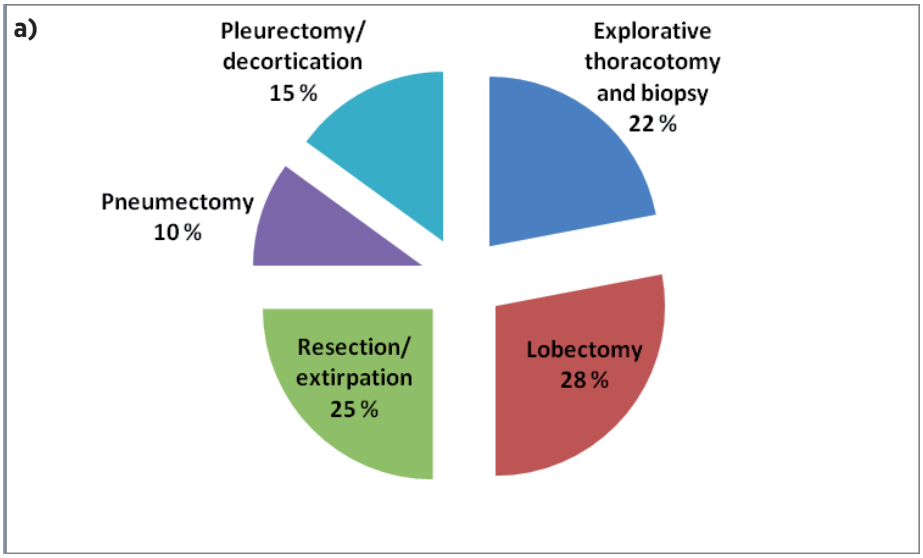
problems. The rest of the patients in the Study II (120 patients, 75%) were healthy, not including gall bladder disease.

The types of the operations in Studies I and IV are presented in Figure 7. Out of the 111 operations in Study I, 19 (17%) were emergency operations. Similarly, out of the 111 operations in Study IV (control group), 13 (12%) were emergency operations.

Table 6. Summary of the demographic and clinical data of patients in studies I, II and IV.

	Study I (n=111)	Study II (n=159)	Study IV/ Intervention group (n=30)	Study IV/ Control group (n=111)
Male/Female (%)	62/38	25/75	43/57	45/55
Age, years, mean (SD)	54 (15)	42 (2)	61 (9)	60 (11)
BMI, mean (SD)	26 (2)	25 (0,5)	25 (3)	26 (2)
ASA status (%)				
I	24	75	13	3
II	28	25	40	9
III	41	0	33	78
IV	7	0	14	10
Malignant/benign disease (%)	65/35	0/100	70/30	83/17
Duration of the operation, min, mean (range)	n.a.	54 (45-61)	156 (71-256)	132 (66-220)
Blood loss during the operation, ml, mean (SD)	320 (210)	50 (15)	240 (174)	220 (164)

BMI=body mass index, n.a.=not applicable



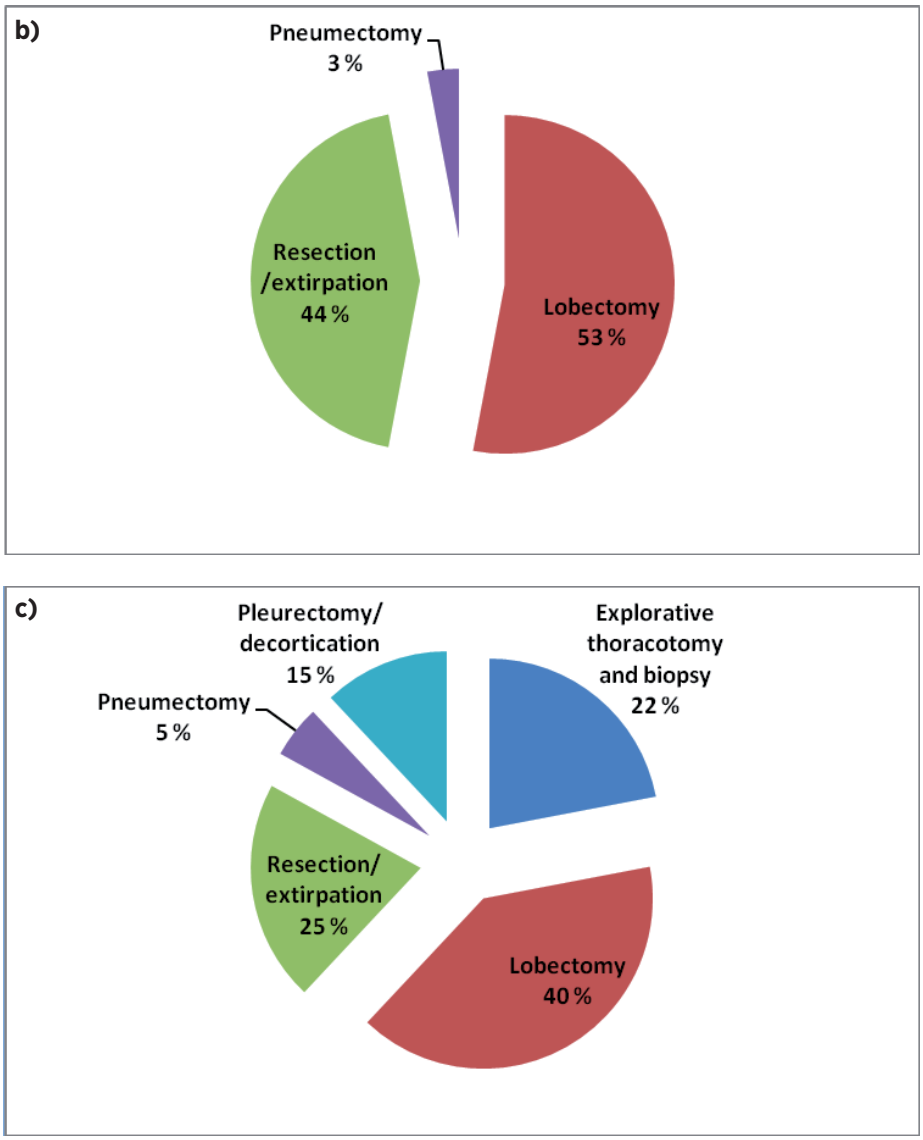


Figure 7. Types of operations (%) in Study I (a), Study IV Intervention group (b) and Study IV Control group (c). Some patients had several procedures during the same surgery and only the main procedure is considered here.

5.2. CHARACTERISTICS OF ANALGESIA IN THORACOTOMY STUDIES I AND IV

A vast majority of the thoracotomy patients were treated with thoracic epidural analgesia in Study I as well as in the control group of Study IV, whereas only one-third of the intervention patients in Study IV received TEA. The duration of

the invasive pain management (TEA or IV-PCA) was significantly longer for the intervention group patients (Study IV) who were involved in the strict study protocol in comparison to the non-randomized patients in Study I and to the standard care patients (control group) in Study IV ($p<0.05$). However, the duration of the pleural drainage was similar for the groups. The control patients in Study IV were discharged significantly earlier than both the intervention patients (Study IV) and the patients in Study I ($p<0.001$). Furthermore, all patients reported being satisfied with their pain management. One-fifth to one-fourth of the patients who were not involved in the controlled pain management protocol (Study I and Study IV/control group) lost their TEA prematurely due to technical problems or to adverse effects, whereas this was not a factor for the patients in the intervention group. For details, see Table 7.

Table 7. Characteristics of perioperative analgesia in thoracotomy Studies I and IV.

	Study I (n=111)	**Study IV/ Intervention group (n=30)**	**Study IV/Control group (n=111)**
TEA/iv-PCA opioid/other treatment	89/18/4 (80%/16%/4%)	10/20 (33%/67%)	104/7 (94%/6%)
Placement of the epidural catheter	Th 4/5 - 7/8	Th 4/5 - 6/7	Th 4/5 - 8/9
Duration of TEA/iv-PCA (days)	5(2)	6(2)	4(2)
Removal of pleural drains (POD)	5(3)	5(3)	4(2)
Day of discharge (POD)	8(4)	8(3)	5(2)
Patients' satisfaction with pain management*			
treatment was good	87%	100%	90%
treatment was satisfactory	13%	0%	10%
treatment was poor	0%	0%	0%
TEA treatment stopped prematurely (total)**	24%	0%	20%
catheter slipped out or did not work	20%	0%	16%
adverse effects	4%	0%	4%

TEA=thoracic epidural analgesia, PCA=patient controlled analgesia, POD=postoperative day.

Mean (SD) or actual numbers given when appropriate.
* In the intervention group patients' satisfaction was assessed with NRS 0-10, and "treatment was good" was equivalent to NRS 8-10/10.
** In the intervention group a new epidural catheter was placed in 1 patient due to the original catheter slipping out.

5.3. PAIN IN THE ACUTE PHASE (STUDIES I, II AND IV)

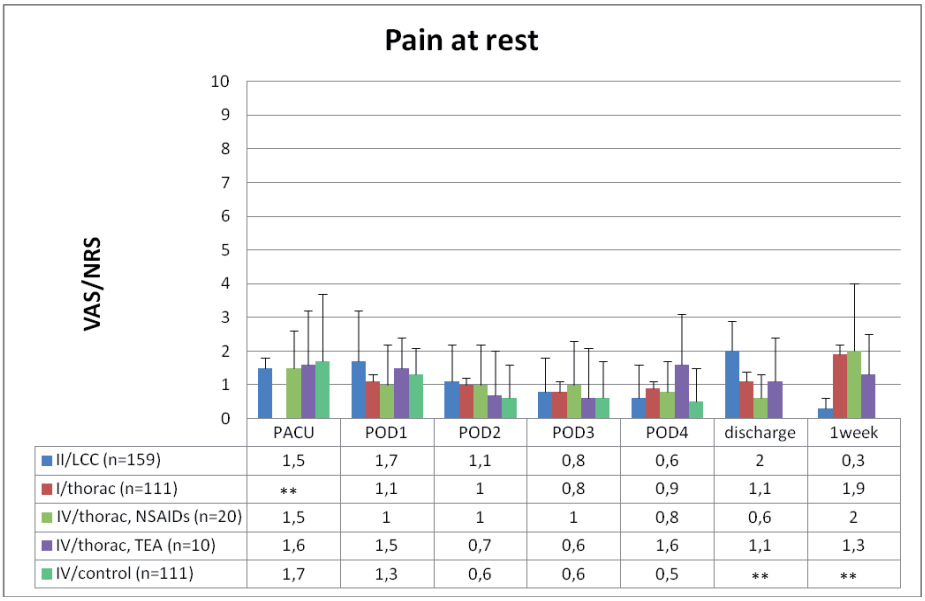
The pain intensity (VAS or NRS) from the PACU to one week after the patient's discharge is presented in Figure 8. During the early postoperative phase in **Study I**, the pain intensity with the IV-PCA patients was NRS 5.7/10 compared to TEA patients whose mean NRS was 4.9/10. The NSAID groups in **Study IV** were combined because the analgesic efficacy was similar between valdecoxib and diclofenac. In comparison, the post-physiotherapy pain on POD 1 was significantly less in the epidural group versus the NSAID group (VAS 2.9 versus 5.0, respectively) ($p<0.05$), and physiotherapy was more successful on POD 3 for the epidural patients ($p<0.05$). Furthermore, the duration of the provoked pain after coughing was longer in the NSAID group than the epidural group. However, the patients in the intervention group who participated in the Study (n=30) and the patients in the control group (n=111) displayed no significant differences in their pain intensity during hospitalization. Half of the intervention patients (16/29) had a measurable area of hyperalgesia in hospital without differences between the subgroups. The patients with hyperalgesia also experienced significantly more pain when coughing in the PACU and on POD 3.

APS was available five days a week for the control patients whereas the intervention patients were seen by the researchers for seven days a week. Furthermore, the control patients did not have the opportunity for close follow-up after discharge other than included in the standard care.

The natural course of pain intensity after ambulatory LCC (**Study II**) is presented in Figure 8. No differences were evident in the pain intensity between the four groups at home. Pain in the right shoulder was a complaint expressed by 30-36% of the patients at home, and it was most intense on POD 1 and continued for several days.

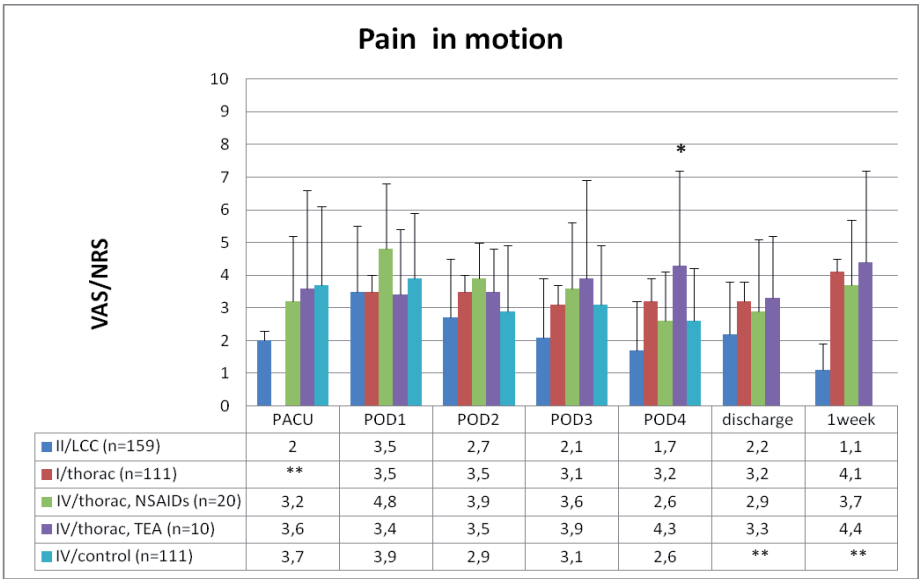
Approximately 30% of the thoracotomy patients in **Study I** had difficulties in their daily activities due to their postoperative pain a week after being discharged from hospital. In **Study IV,** no significant difference in the pain intensity was detected between the NSAID and TEA groups. Out of the 30 patients, pain disturbed the daily activities of 7 patients (23%), and 14 patients (47%) had difficulties in sleeping due to their pain.

a)



	PACU	POD1	POD2	POD3	POD4	discharge	1week
II/LCC (n=159)	1,5	1,7	1,1	0,8	0,6	2	0,3
I/thorac (n=111)	**	1,1	1	0,8	0,9	1,1	1,9
IV/thorac, NSAIDs (n=20)	1,5	1	1	1	0,8	0,6	2
IV/thorac, TEA (n=10)	1,6	1,5	0,7	0,6	1,6	1,1	1,3
IV/control (n=111)	1,7	1,3	0,6	0,6	0,5	**	**

b)



	PACU	POD1	POD2	POD3	POD4	discharge	1week
II/LCC (n=159)	2	3,5	2,7	2,1	1,7	2,2	1,1
I/thorac (n=111)	**	3,5	3,5	3,1	3,2	3,2	4,1
IV/thorac, NSAIDs (n=20)	3,2	4,8	3,9	3,6	2,6	2,9	3,7
IV/thorac, TEA (n=10)	3,6	3,4	3,5	3,9	4,3	3,3	4,4
IV/control (n=111)	3,7	3,9	2,9	3,1	2,6	**	**

Figure 8. Pain intensity (VAS/NRS 0-10) at rest (a) and in motion (b) in studies I, II and IV. Mean (SD) are given. PACU=postanaesthesia care unit at 3-4h, LCC=laparoscopic cholecystectomy, TEA=thoracic epidural analgesia, thorac=thoracic surgery, POD=postoperative day (assessed in the afternoon), discharge=day when the patient was discharged from hospital (the day of surgery in day-case LCC patients), 1week=1 week after discharge. **= not applicable. One week information was collected from thoracotomy patients by phone and from LCC patients by a questionnaire. * = On POD 4 the TEA patients in study IV had significantly more pain when coughing compared to NSAID and Control patients ($p<0,05$).

5.4. CONSUMPTION OF ANALGESICS IN THE ACUTE PHASE (STUDIES I, II AND IV)

5.4.1. IN HOSPITAL

In **Study IV**, the IV-PCA opioid consumption was similar in the diclofenac and coxib groups [mean (SD) were 35 mg (12) and 34 mg (13) per day, respectively]. Furthermore, there were no differences in a need for supplemental oxycodone after PCEA/PCA. Most of the patients in the control group (94%) had TEA, and all of them were administered NSAIDs or paracetamol, or both. Additionally, half of the patients needed regular weak opioids after TEA/PCA.

In the management of pain after ambulatory LCC in **Study II,** paracetamol was as effective as pare-/valdecoxib. The time until the first dose of oxycodone in Phase 1 PACU was similar in the four groups (mean 14 minutes, SD 2), as was the total amount of oxycodone required (mean 12 mg, SD 1). Dexamethasone decreased the need for oxycodone in Phase 2 PACU just prior to discharge, but this opioid-sparing effect was similar in both paracetamol- and coxib-treated patients. The mean oxycodone consumption was 9.1 mg (SD 1.0) in the groups without dexamethasone as compared to 7.0 mg (SD 1.0) in the groups with dexamethasone ($p<0.05$).

5.4.2. DURING THE FIRST WEEK AT HOME

In **Study I**, during the first week at home after being discharged 92% of the patients required analgesics daily. Ibuprofen 600 mg or paracetamol 1 g was taken regularly three times a day by 86% and tramadol 100 mg three times a day by 71% of the patients. Sixteen per cent of the patients needed renewed prescriptions of analgesics since the original amount was not deemed to be sufficient. One- fifth of the patients needed instructions on how to take pain medication a week after discharge, and the same percentage of patients phoned the APS nurse when they encountered problems with pain. Furthermore, one patient in ten felt that the change from epidural to oral pain treatment was too dramatic and that they were discharged prematurely while they still had unacceptable pain. When comparing the control patients with the intervention patients in **Study IV,** only 23% of the control patients were prescribed weak opioids with NSAIDs/ paracetamol for home, whereas 100% of the intervention patients received them. Moreover, one week after discharge, 77% (23/30) of the intervention patients needed weak opioids daily in addition to NSAIDs, and 23% (7/30) patients needed a renewed prescription for tramadol (versus 71% and 16% in Study I, respectively).

Significantly more patients in **Study II** in both the coxib-treated groups (Groups 1 and 3) needed additional rescue analgesics on POD 1 and POD 4 than the patients who were given paracetamol ($p<0.01$ on POD 1 and $p<0.05$ on POD

4). Subsequently, however, that difference receded. Almost half of the LCC patients still required some type of analgesic medication one week after being discharged, but no one needed weak opioids.

5.5. PERSISTENT PAIN AFTER THORACIC SURGERY (STUDIES I AND IV)

Figure 9 represents the intensity of post-thoracotomy pain and the impact it has on daily life and sleep three and six months after thoracic surgery.

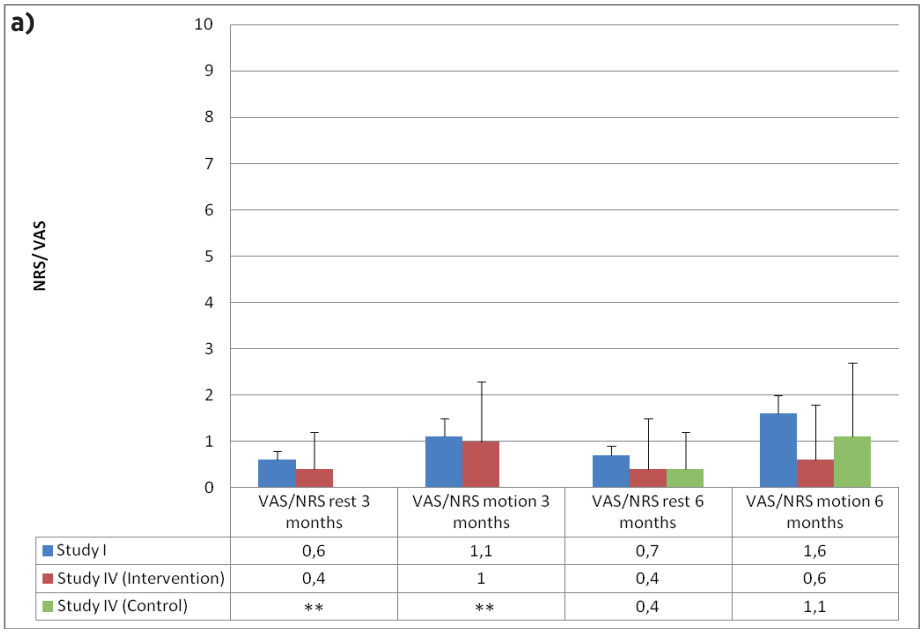
5.5.1. THREE MONTHS AFTER THORACOTOMY

Study I found that at 3 months, 8 TEA-patients (11%) and 4 PCA-patients (29%) experienced disturbing chronic pain (see the definition in Figure 8), and 40% of the patients in both groups were completely free of pain. The reported pain was predominantly tenderness or aches, but numbness (45%), burning pain (10%) and lancinating pain (2%), as signs of possible intercostal neuralgia were also detected Furthermore, when patients with or without persistent pain were compared three months after surgery, there was no significant difference in the pain intensity on the day of discharge between the groups. Instead, the cumulative consumption of epidural fentanyl was somewhat higher on PODs 1-3 in the patients who had persistent pain at 3 months (P=0.06) when compared to those who were free of pain. In **Study IV,** at 3 months, half (15/30) of the intervention group patients still needed daily analgesics.

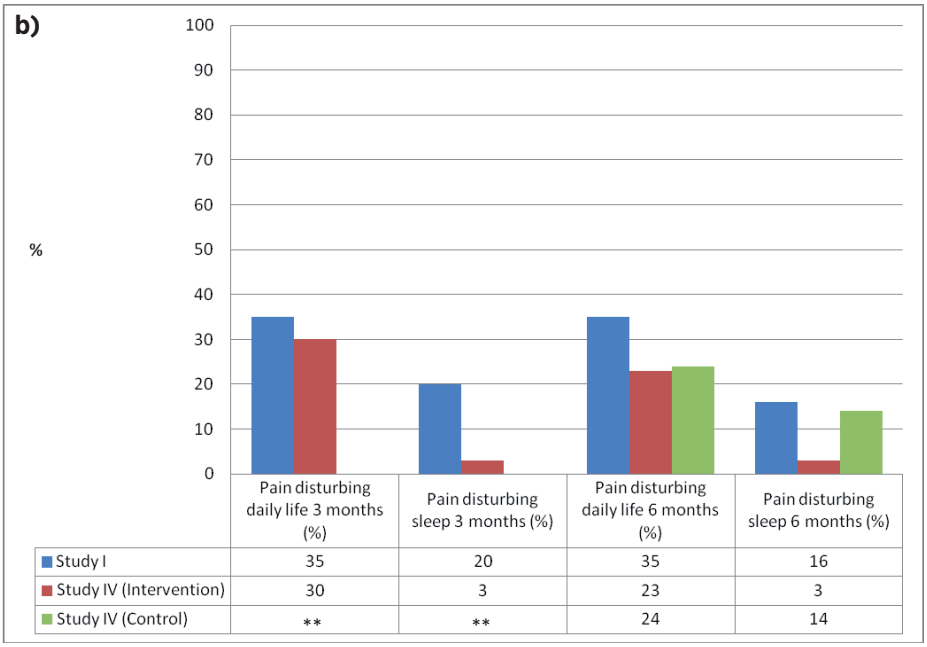
5.5.2. SIX MONTHS AFTER THORACOTOMY

In **Study I**, 7 (12%) of the TEA patients and 3 (23%) of the IV-PCA patients experienced persistent pain 6 months after the thoracotomy. One patient reported severe pain, none of the patients had excruciating pain. Out of all patients, 21% were taking analgesics daily and 15% on a weekly basis. Weak opioids were needed by 20% of the patients as long as 6 months after the thoracotomy. Seventeen per cent of the patients had experienced pain for less than 3 weeks, 17% from 3 weeks to 2 months, and 16% from 2 to 5 months.

In **Study IV,** persistent pain 6 months after the thoracotomy was more common in the control patients than in the patients in the intervention group (24% versus 3%, respectively) ($p<0.001$). Out of the 111 patients, 25 patients in the control group (25%) needed daily analgesics compared to 2 (7%) out of the 30 patients in the



	VAS/NRS rest 3 months	VAS/NRS motion 3 months	VAS/NRS rest 6 months	VAS/NRS motion 6 months
Study I	0,6	1,1	0,7	1,6
Study IV (Intervention)	0,4	1	0,4	0,6
Study IV (Control)	**	**	0,4	1,1



	Pain disturbing daily life 3 months (%)	Pain disturbing sleep 3 months (%)	Pain disturbing daily life 6 months (%)	Pain disturbing sleep 6 months (%)
Study I	35	20	35	16
Study IV (Intervention)	30	3	23	3
Study IV (Control)	**	**	24	14

Figure 9. Mean intensity (SD) of persistent pain at 3 and 6 months expressed as NRS/VAS (a) and incidence of persistent pain (%) which disturbs daily life and sleep (b) (Studies I and IV). NRS=numeric rating scale 0-10; VAS=visual analogue scale 0-10; Intervention=intervention group in Study IV (NSAID group + epidural group, n=30); Control=Control group in Study IV (standard care patients, n=111). In Study I only patients treated with epidural analgesia are involved in the figure (n=73 at 3 months and n=65 at 6 months). Chronic pain was defined as VAS/NRS>3/10 and as "moderate", "severe" or "excruciating" on the verbal rating scale (VRS), and it disturbed daily life and/or sleep.

intervention group (p<0.001). Twenty-one patients in the control group needed weak opioids and four needed strong opioids, which were prescribed to three patients with benign disease. No one in the intervention group needed opioids at this time point. Furthermore, in those control patients who developed persistent pain, their pain was significantly more intense when coughing on POD 3 (mean VAS 4.1, SD 2.0). Hyperalgesia did not, however, predict prolonged pain. The only patient with persistent pain at 6 months (the coxib group) had a considerably longer duration of pain after coughing (60 seconds on POD 3) than other intervention patients (median 2 seconds, range 0-6).

5.6. ADVERSE EFFECTS (STUDIES I, II AND IV)

The adverse effects in the clinical Studies I, II and IV are presented in Table 8. Among all the thoracotomy patients in Studies I and IV, two patients in Study IV/control group with epidural treatment had severe respiratory depression and needed mechanical ventilation. No differences emerged in Study IV between the parecoxib or valdecoxib, diclofenac and epidural groups regarding their cardiorespiratory, bowel and urinary functions, diuresis, blood loss, creatinine and cystatine-C levels.

Table 8. Adverse effects in Studies I, II and IV.

Adverse effect	Study I/ TEA	Study I/ PCA	Study IV/ Int., TEA	Study IV/Int., NSAID+PCA	Study IV/Control	Study II
Nausea[1]	15%	28%	10-30%	10-25%	18%	3%
Tiredness[2]	n.a.	n.a.	40-45%	30-45%	24%	n.a.
Dizziness/ drowsiness	4%	11%	n.a.	n.a.	n.a.	7%
Pruritus	13%	0	30%	5%	17%	0
Hypotension[3]	2%	0	0	0	5%	0

TEA=thoracic epidural analgesia; PCA=patient controlled analgesia; Int.=Intervention group; n.a.=not applicable. Studies I and IV=thoracotomy patients; Study II=day-case LCC patients.

[1] Needed medication for nausea; all of these patients in the control group had epidural analgesia; Differences between IV/intervention vs. IV/control groups and between NSAID+PCA vs epidural patients=NS; LCC patients who suffered from nausea needed to stay overnight in hospital.
[2] NRS>5/10; all of these patients in the control group had epidural analgesia.
[3] Hypotension which needed adjustment of treatment or medication.

5.7. RESULTS OF STUDY III

This systematic review included a total of 22 randomized, controlled, double-blind clinical trials of the perioperative administration of gabapentin or pregabalin for postoperative pain relief. The total number of patients was 1 909, of which 786

received gabapentin (21 studies) and 99 received pregabalin (1 study). The patients' ages ranged from 18 to 74 years, 1 265 were women and 509 were men.

The doses of gabapentin administered to the patients were 300-1200 mg and for the pregabalin study, the doses were 50 mg or 300 mg. A single dose was administered in 13 studies and multiple doses were administered in 9 studies. The duration of the trials ranged from 4 hours to 10 days. In the only trial with pregabalin, the drug was administered postoperatively after dental surgery, and regarding the patients' satisfaction with their pain relief and duration of analgesia, 300 mg of pregabalin was determined to be more efficient than 400 mg of ibuprofen.

5.7.1. ANALGESIA

The pain relief was significantly better in the gabapentin groups than in the control groups. For the different types of surgery, the difference in pain intensity varied widely between the control and gabapentin groups at rest and in motion during the first 24 hours after a single 1200 mg dose of gabapentin administered 1-2 hours preoperatively, and the pain intensity difference was greatest after a discectomy and a hysterectomy. The time for the first analgesic request was reported in 5 of the 22 studies, and 2 of these studies detected a difference that favoured 1200 mg of gabapentin over the placebo.

After a single preoperative dose of 300-1200 mg of gabapentin, the opioid-sparing effect during the first 24 hours ranged from 20% to 62%. A meta-analysis revealed that the combined effect of a single dose of gabapentin on opioid consumption was equivalent to a reduction of 30±4 mg in morphine (mean±95% CI) consumed during the first 24 hours postoperatively. Figure 3/Study III displays the weighted mean differences (WMDs) with the 95% CI and the combined effect of gabapentin on the patients' opioid consumption. Whereas the heterogeneity among the studies was significant, it was not due to the dose of gabapentin.

When the administration of gabapentin continued two to ten days after surgery, five trials reported long-term effects. The follow-up ranged from one to six months. Three studies concentrated on abdominal hysterectomies and two on mastectomies. For acute pain, four of the five studies favoured gabapentin to the placebo, and two of these studies found a difference in chronic pain, whereas the other two did not.

5.7.2. ADVERSE EFFECTS

After a single dose of 1200 mg of gabapentin was administered 1-2 hours preoperatively, the numbers-needed-to-treat (NNT) to prevent nausea, vomiting or urinary retention during 20-24 hours after surgery, were 25, 6, and 7, respectively.

The numbers-needed-to-harm (NNH) for gabapentin to produce excessive sedation or dizziness were 35 and 12, respectively. No significant differences in other adverse effects were reported.

5.7.3. ANXIOLYTIC EFFECTS

Two trials analyzed the anxiolytic properties of gabapentin. In one study, premedication with gabapentin produced significantly lower preoperative VAS anxiety scores than the placebo (212). The second study determined that 15 mg of oxazepam was more effective in relieving preoperative anxiety than 1200 mg of gabapentin (217).

5.8. RESULTS OF STUDY V

The baseline measurements in this experimental study were similar between the sessions and the study groups. In Study 1, paracetamol 2 g IV did not produce any statistically significant analgesic effects in either the patients' heat or cold pain intensities or in their cold pain tolerance. In Study 2, paracetamol alone did not produce any differences in sensory, pain detection or in the moderate pain thresholds of the electrical stimulus with Pain Matcher. However, when the percentage scores were calculated according to Pickering et al. (29), an analgesic effect was detected for the combination of paracetamol and tropisetron (Figure 3/Study V). This means that contrary to Pickering's findings, tropisetron seemed to amplify the analgesic action of paracetamol. Nonetheless, conclusions concerning any possible interaction between paracetamol and tropisetron cannot be drawn based on these volunteer studies.

6. DISCUSSION

This thesis evaluated the intensity of acute post-thoracotomy pain and the incidence of chronic pain after thoracic surgery in two studies, including the possibilities of managing pain in the acute phase as well as in the sub-acute phase at home. To prevent acute and persistent post-thoracotomy pain, the extended protocol for the high quality pain management in hospital, also covering the first week at home after the patient's discharge, was found to be more significant than any particular analgesic technique in itself. The importance of a strict pain management protocol was also observed after ambulatory LCC in the acute phase. This was an antiemetic anaesthetic technique that involved multimodal pain treatment with NSAIDs/paracetamol + corticosteroids as opioid-sparing analgesics that enabled 95% of the patients to be discharged on the day of surgery. In addition, the opioid-sparing and pain alleviating role of the gabapentinoids in the acute postoperative phase was demonstrated in a systematic review. According to an experimental volunteer study, the previously suggested interaction in which tropisetron abolishes the analgesic action of paracetamol, could not be investigated due to the lack of a measurable analgesic effect of paracetamol.

6.1. SELECTING THE RIGHT METHOD OF PAIN MANAGEMENT

Several factors influence the evaluation of the best method for postoperative pain management. For example, invasive methods (neuraxial blocks with catheters, IV-PCA) are strongly recommended after very painful operations, such as a thoracotomy (47, 50, 100, 101, 103, and Studies I & IV), and in the surgery of the upper abdomen. However, patients who undergo day-case surgery do not particularly benefit from invasive methods, as these would increase the time and costs of their perioperative care, not to mention the risk of side-effects. Instead, multimodal pain management utilizing adjuvant analgesics, such as dexamethasone can be warmly recommended especially in day-case LCC (136, Study II). Table 9 lists the factors that need to be considered when determining the best method of pain management for an individual patient.

Table 9. Factors influencing the choice of the method of postoperative pain management.

Patient related factors	Age BMI (sleep apnoea, technical difficulties in placing epidural catheters, etc.) Risk factors for chronic post-surgical pain (see Table 4) Anticoagulation, other medications (e.g. long-term opioid use) Preference of the patient
Factors related to the type of surgery	Major/minor surgery Thoracoscopic/open thoracotomy Laparoscopic/open abdominal surgery Upper/lower abdomen Orthopaedic surgery and mobilization Risk of nerve damage
Patient monitoring possibilities	PACU/ ICU/ surgical ward APS APS follow-up outpatient clinic
Time of discharge from hospital	Day-case surgery Fast-track surgery Longer hospitalization

BMI=body mass index; PACU=postanaesthesia care unit; ICU=intensive care unit; APS=Acute pain service

6.2. ACUTE AND PERSISTENT POST-THORACOTOMY PAIN

6.2.1. TRANSITION FROM ACUTE TO CHRONIC POSTSURGICAL PAIN

The progression from acute to chronic pain is a complex phenomenon, involving an association with various risk factors that are surgical, psychosocial, socio-environmental and patient-related, as well as the known polymorphisms in human genes (4, 5, 179; Table 4). Postoperative pain consists of pain that is somatic, inflammatory, neuropathic and visceral, and it triggers a stress response that activates the central nervous system. Local tissue injury also leads to the spontaneous firing of nociceptors and their increased sensitivity to stimuli (primary hyperalgesia). This continued input from the perioperative noxious injury barrage by severe acute pain may lead to changes in the central nervous system, resulting in sensitization and pain from a wider area (secondary hyperalgesia). This phenomenon is a dynamic reflection of the central neuronal plasticity, "a pain memory", which is considered to be the basis for chronic postsurgical pain. These long-term neurobiological changes occur rather rapidly, even within hours of an acute injury (174, 178). However, most

of the analgesics that are used to alleviate postoperative pain are not very effective for secondary hyperalgesia.

Most clinical studies on acute postsurgical pain have focused primarily on the acute phase when patients are still in hospital. However, few studies provide data on the *sub-acute phase* when patients are at home recovering and are rehabilitating from surgery. During this phase, central sensitization continues, bridging the transition from acute to persistent postoperative pain. Two thoracotomy studies in this thesis (I, IV) offer some information regarding the pain and the condition of the patients one week after being discharged from hospital.

6.2.2. MANAGEMENT OF ACUTE PAIN AFTER THORACOTOMY IN STUDIES I AND IV

During the time between Studies I and IV, thoracic epidural analgesia has been established in the management of acute pain after thoracotomy. In the beginning of the 21st century (Study I), 80% of the patients were treated with TEA, 16% with IV-PCA and 4% with conventional methods, such as a single-shot intercostal nerve block and intramuscular oxycodone, and NSAIDs/paracetamol as basic medication. At the end of the past decade (Study IV), however, 94% of the patients had TEA and 6% IV-PCA. This indicates that conventional "low-tech" methods were no longer acceptable due to their inferior efficacy in pain management.

Thoracic epidural analgesia has demonstrated its superiority in both thoracotomy studies, particularly in the treatment of dynamic, evoked pain. This finding is consistent with recent literature (see Thoracotomy 2.3.1.). Physiotherapy was also more successful in the epidural group, and the duration of pain after coughing was shorter (Study IV). One unexpected outcome was that the pain treatment in all the intervention groups provided sufficient analgesia for physiotherapy.

6.2.3. PERSISTENT POST-THORACOTOMY PAIN IN STUDIES I AND IV

In the two thoracotomy studies, the incidence of chronic pain 6 months after surgery was somewhat lower than described in the literature, ranging from 3% to 24% as compared to the usual incidence of 5-65%. According to the first thoracotomy study, 12% of the TEA patients and 23% of the IV-PCA patients had disturbing pain 6 months after surgery. This comparison of methods was not possible in the second thoracotomy study because only 1 patient in the intervention group (coxib + IV-PCA) had chronic pain after 6 months, compared with 24% of the patients in the control group.

According to Studies I and IV, the combination of thoracic epidural analgesia and extended postoperative pain management at home may decrease the occurrence of chronic post-thoracotomy pain. Some evidence suggests that TEA could prevent central sensitization, but this finding remains controversial (11, 155). Blocking the neuronal pathway during surgery with epidural local anaesthetics does not decrease humoral biochemical responses (for example, prostaglandin E2 and interleukins), which must be inhibited by systemic analgesics (218). In a meta-analysis conducted by Bong et al. (197), pre-emptive TEA appeared to reduce the severity of acute pain without any effect on the incidence of chronic pain. By contrast, in Study IV, those patients who had hyperalgesia also had more pain when coughing. However, conclusions cannot be drawn regarding whether hyperalgesia could predict persistent post-thoracotomy pain, as only one patient in the intervention group had persistent long-term pain.

In the prevention of acute as well as persistent post-thoracotomy pain, it is possible that the continuous high quality patient care in the acute phase covering at least the first week at home could be more significant than any particular analgesic method *per se*. However, it is important to ensure that the effective preventive analgesic regimen is continued into the sub-acute phase in the post-discharge period. This means for as long as the nociceptive input from the wound area persists after surgery – approximately 4-6 weeks postsurgery. This phenomenon has also been suggested after hip or knee replacement surgery, where the superior analgesic regimen and follow-up after discharge also reduced chronic pain when compared to standard-of-care analgesia (219). After thoracotomy, eight per cent of patients had neuropathic pain in the immediate postoperative period in hospital, but this proportion was increased to 22% after 3 months (220). If the patient continues to have moderate to severe pain on the day of discharge, neuropathic features of pain, and needs several different pain medications, the anaesthesiologist should follow-up after 1-3 weeks by phone or by appointment in order to recognize the patients who need further treatment (221). This type of experimental "post-surgery APS follow-up outpatient clinic" has recently been established at the Helsinki University Central Hospital.

6.2.4. WHAT IS THE BEST ANALGESIC METHOD FOR THORACOTOMY PATIENTS?

The role of thoracic epidural analgesia as the gold standard in acute post-thoracotomy pain is slowly diminishing. The reason for this decrease in usage is that it is a technique that is invasive, costly and labour-intensive, and the rare but potentially disastrous complications (epidural hematoma and abscess) cannot be ignored (222). There is no doubt that with functioning TEA, the pain relief can be

excellent, but the risk for adverse effects compared with the benefits of this invasive technique should be carefully considered in low-risk patients.

IV-PCA with strong opioids, combined with NSAIDs/ paracetamol and single-shot intercostal nerve blocks with local anaesthetics, offers acceptable pain relief after thoracotomy, especially at rest (Studies I and IV). High-risk patients who suffer from pulmonary and cardiac disease and/or massive obesity with sleep apnoea were excluded from these studies. Altogether, the risk-benefit ratio of these patients clearly favours TEA, which is also superior when assessing the outcomes after high-risk surgery, such as esofagectomy (223). Opioid-sparing adjuvants, such as gabapentinoids, epidural clonidine and adrenaline or systemic ketamine, may be administered to patients who have re-thoracotomy, pre-existing chronic pain in the surgical area, problems in tolerating opioids or those with a background of narcotics abuse. However, convincing evidence is still lacking concerning the efficacy of gabapentinoids for acute post-thoracotomy pain or for their ability to prevent persistent pain, even though their antihyperalgesic mechanism of action is promising. In addition, intrathecal opioids for thoracotomy patients are not administered in our hospital due to their short time span (24 hours) and due to the increased risk for respiratory depression that cannot be sufficiently monitored in the surgical ward.

Another safe and effective alternative to TEA after thoracotomy is the paravertebral block (PVB) with an infusion of local anaesthetics (166-168, 224). This non-invasive method is also feasible in anticoagulated patients when the surgeon places the catheter before closing the wound. The action of PVB needs intact pleura to form an anterior limit to the paravertebral space and it cannot be used with empyema patients whose pleura has been removed by surgical decortication.

Figure 10 presents one suggestion for the management of acute post-thoracotomy pain.

6.2.5. APS

When invasive pain management methods are used, APS is strongly recommended. The APS nurses and anaesthesiologists secure the safety of continuous epidural and peripheral nerve blocks, supervise IV-PCA techniques, and are responsible for ongoing educational programmes for all those involved in postsurgical pain management. These nurses and anaesthesiologists also supervise and audit the monitoring of acute pain and the effects of pain relief. In other words, they make pain visible. Another benefit is that APS has also been shown to be cost-effective (108-110).

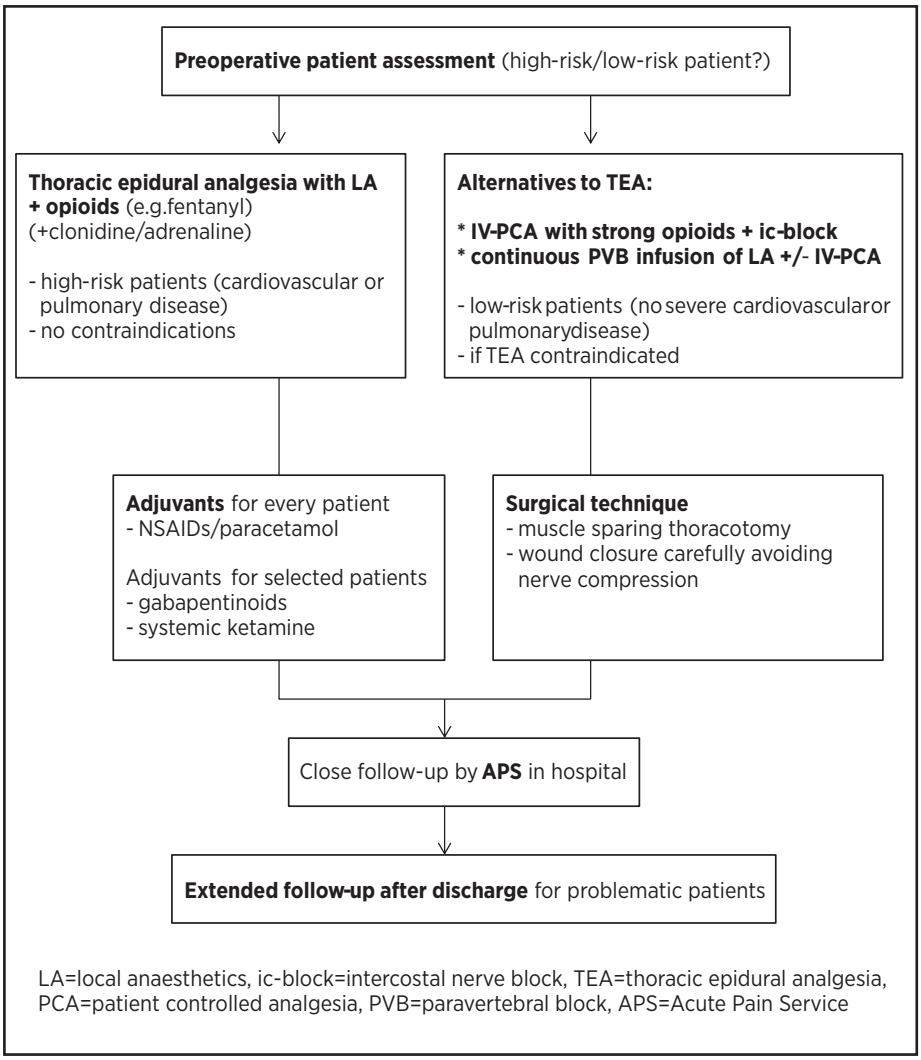


Figure 10. A recommendation for postoperative pain management for thoracotomy.

In Study IV APS was available only five days a week for the patients in the control group whereas the patients in the intervention group were seen by the researchers every day. Out of the patients in the control group, 76% spent one weekend at hospital without the close follow-up of APS. The control patients were discharged after five days, which is significantly earlier than the intervention patients (eight days). Thus, the intervention patients received more intensive pain management for significantly longer, which may partially explain their lower incidence of persistent pain.

6.3. PARTICIPANTS IN THE CLINICAL TRIALS VERSUS THE "AS USUAL" CONTROLS

In Study IV, persistent post-thoracotomy pain was significantly more prevalent among the control patients than the intervention patients (24% versus 3%, respectively). It seems that the standard care is not sufficient in preventing chronic pain after thoracic surgery, since the insufficient relief of acute pain may predispose a patient to persistent postsurgical pain. As regards to Study IV, it was a rather novel idea to include the standard care patients who were not involved in the intervention study in the control group. Patients who participate in an RCT are carefully selected and they may not represent the whole patient population. Moreover, patients in an RCT receive extra attention, and that treatment may therefore be better than ordinary care. Based on these facts, it is important to compare how the results in an RCT correlate with those of the standard care patients. Furthermore, something resembling a "Hawthorne effect" occurs when the routine care is improved within the trial (225).

It has been suggested that participating in an RCT is likely to produce similar outcome results as similar treatment outside the trial. This means that the results of RCTs can be applied to usual clinical practice (226, 227). However, the pain management and the follow-up of the trial participants may differ significantly from those of standard care patients, and that is why comparing the outcomes between these groups is informative. This data can be utilized to improve the practice of pain management protocols.

In Study IV, the control group consisted of patients not eligible to the intervention study, with contraindications to the interventional analgesic methods, significant liver, renal or cardiac disease, regular use of analgesics, re-thoracotomy, and emergency operation. These patients were treated with standard care of the hospital, and the groups differed quite a lot. The control patients may have been more diseased than the intervention patients, and emergency operations put some challenges to the pain management. Eighty-eight per cent of the controls were operated electively, yet. However, psychological vulnerability is thought to be more important risk factor for chronic postoperative pain than physical illness (Table 4).

6.4. CAN WE PREDICT ACUTE AND CHRONIC POSTSURGICAL PAIN?

In order to prevent patients from having pain that is severe, acute and persistent, it is crucial to identify those patients who are at high risk before they undergo surgery. Some predisposing factors for developing chronic post-surgical pain are listed in Table 4, and some of these (type of surgery, age, psychological distress

and catastrophising) are also significant predictors for acute postoperative pain and analgesic consumption (228). In Study I, the cumulative consumption of epidural fentanyl was somewhat higher postoperatively in those patients who had chronic pain three months after surgery, which is consistent with the literature on this subject.

Surgery induces peripheral neural activation with central neuroplastic changes. In some patients, these phenomena may occur during the transition into a state of persistent postoperative pain. The pain threshold reveals the transition point where a painless sensation changes to a painful one. The suprathreshold painful stimuli – a sensation between the pain threshold and tolerance – may better mimic the pain experience that is caused by surgery. In a systematic review (229), pain stimuli were applied that were thermal, pressure and electrical, suggesting that the high levels of pain intensity that is evoked by a suprathreshold heat stimulus were most consistently associated with the stronger postoperative pain of female patients. Furthermore, the preoperative quantitative sensory testing (QST) may predict persistent postoperative pain, as has been suggested with thoracotomy patients. In addition, less efficient diffuse noxious inhibitory control (DNIC, see 2.5.1.) and enhanced temporal summation (increasing pain scores after repetitive stimuli) have been demonstrated to predict acute and chronic post-thoracotomy pain (230-232). An electrical stimulus induced by Pain Matcher (see 4.3.2.), which was also used in Study V, may also have some predictive value as a screening tool to identify the patients who are at high risk of acute and persistent postoperative pain (233-235).

Study IV assessed hyperalgesia using two methods: by measuring the hyperalgesic area around the scar with a von Frey hair (210), and by a "coughing test", which was introduced as a new measure of hyperalgesia in post-thoracotomy pain (see 4.4.1.). Half of the patients in the intervention group had a measurable area of hyperalgesia before their discharge and they also had more pain when coughing than those who did not have hyperalgesia. However, hyperalgesia did not predict persistent pain. Nonetheless, no conclusions can be drawn from this, since the test group was so small, and only one patient in that group experienced long-term pain. The duration of pain that was assessed after coughing was longer in the NSAID group than in the epidural group. The only patient with persistent pain 6 months after the surgery had a considerably longer-lasting pain in the coughing test than the other patients (60 seconds versus a median of 2 seconds). This type of "coughing test" needs to be validated in a larger RCT to determine whether it is clinically valuable.

By identifying the patients who are at risk of severe, postoperative acute and chronic pain, we will be able to offer them more effective pain management that is individually tailored. Another benefit of determining those patients at risk is that we can avoid using unnecessary invasive pain treatment methods and analgesics with potential adverse effects. At present, preoperative genetic or the QST tests are not clinically practical to identify patients at risk. Sipilä et al. (236) have recently

studied the identification of preoperative risk factors for developing chronic pain after breast cancer surgery. Factors that predicted significant pain six months after surgery were preoperative chronic pain, more than four previous operations, preoperative pain in the surgical area, high body mass index, smoking and advanced age. One feasible method to determine which patients would be in need of invasive pain management would be to administer a simple electronic questionnaire by email to patients that explores the preoperative risk factors of persistent pain, especially anxiety and catastrophising. These patients could be invited to see the anaesthesiologist preoperatively. Postoperatively, the screening of hyperalgesia by administering "a coughing test" and the recording of the pain intensity and analgesic consumption would help the APS trace the patients who would benefit from a longer and a closer follow-up.

6.5. GABAPENTINOIDS AS PERIOPERATIVE ADJUVANTS

6.5.1. GABAPENTIN AND PREGABALIN

The systematic review of gabapentinoids for perioperative pain control (Study III) reveals that the pain relief was significantly better in the gabapentin groups than in the control groups. The opioid-sparing effect during the first 24 hours after a single preoperative dose of 300-1200 mg of gabapentin ranged from 20-62%, and the combined effect was equivalent to a reduction in 30± 4 mg of morphine. These findings are consistent with most other systematic reviews that investigate single preoperative doses and the 24-hour effect (115-120). In this current review of gabapentinoids, 9 out of 22 studies examined the multiple dosing of gabapentin.

The main finding of Study III is that the analgesic and opioid-sparing effect was improved by increasing the preoperative gabapentin dose from 300 mg to 600-1200 mg, but this improvement was not found for higher doses. After spinal surgery, a preoperative dose of 22 mg/kg (about 1200-2000 mg) was required for analgesia (122). In a recent Cochrane review (121), gabapentin 250 mg was statistically superior to a placebo when administered for already established acute postoperative pain, but the NNT of 11 was considered of limited clinical value. This review consisted of four unpublished studies with a minor drug dose, and gabapentin was used as a stand-alone analgesic for acute pain.

As a presurgical premedication, the anxiolytic action of gabapentin was controversial in Study III. Whereas a dose of 1200 mg was significantly better than the placebo (216), it was not as effective as oxazepam (217). Yet recently the valuable effect of gabapentin as an anxiolytic premedication has been supported (237). For instance, in a review conducted for the present analysis, pregabalin was used in only one study, and it was used to treat the established pain after dental surgery (238). In addition, concerning the analgesic efficacy of pregabalin, a high dose of 300 mg

was also reported to be superior to 400 mg of ibuprofen (238). Recent literature has also provided evidence that pregabalin produces a dose-related reduction in postoperative opioid consumption (123), with an efficient dose of 225-300 mg/day postoperatively (125). However, this relatively high dose without stepwise titration (as in chronic pain) may be at the expense of adverse effects. The beneficial effects of pregabalin in acute postoperative pain is suggested to be dependent on the type of surgery. In other words, the more acute neuropathic pain, the more useful pregabalin is (124, 127, 128). Despite these results, in a Cochrane review by Moore et al. (126), no clear evidence has been found for the beneficial effects of pregabalin in acute postsurgical pain.

A review by Weinbroum (239) offers the most recent evidence of administering gabapentin and pregabalin for acute postoperative pain. When given as adjuvants to anaesthesia, gabapentinoids are effective in reducing both pain intensity and opioid consumption after surgery. However, their analgesic potential *per se* in comparison with other postoperative analgesics is still not clear, and it is difficult to extrapolate from one study to another due to the heterogeneity of the operations and the varying postoperative requirement of opioids. To reduce anxiety, gabapentin doses of 600-1200 mg and pregabalin 150-300 mg preoperatively have been effective. Nevertheless, White et al. (240) reported an increased sedation but not a reduced state of anxiety before day-case surgery. This was possibly caused by the short time between pregabalin and the induction of anaesthesia (60-90 min), and the relatively low baseline levels of anxiety in the patients undergoing minor surgery.

The most common transient adverse effects caused by gabapentinoids include somnolence and dizziness, headaches, balance problems, peripheral edema, sweating, dry mouth, blurred vision, and gastrointestinal symptoms. The severity of these problems is generally time- and dose-related (239). According to Study III, the numbers-needed-to-harm for gabapentin to produce excessive sedation or dizziness were 35 and 12, respectively, and there was some indication of gabapentin preventing nausea, vomiting and urinary retention.

Table 10 presents a summary of the characteristics of the gabapentinoids for acute pain**.** It should be noticed that it is not possible to provide the definitive recommendations for the dosing.

6.5.2. DO GABAPENTINOIDS PREVENT CHRONIC POSTOPERATIVE PAIN?

According to Study III, five trials reported long-term effects when gabapentin administration was continued two to ten days postoperatively, with the follow-up being from one to six months. Four studies favoured gabapentin to placebo in acute pain, and in two of these studies, it was suggested that gabapentin prevents chronic pain.

Table 10. Comparative summary of gabapentin and pregabalin for acute pain. Adapted from Tiippana et al. (Study III), Zhang et al. (123), Engelman & Cateloy (125), and Weinbroum (239).

Parameters	**Gabapentin**	**Pregabalin**
Absorption	Ceiling effect	Linear
Bioavailability	30-60%	>90%
Plasma protein binding	<3%	0
Metabolism	None	None
Drug interactions	Unlikely	None
Elimination half-life (hours, range)	4.8-8.7	5.5-6.3
Relative potency	1	5-6
Mode of administration	oral, t.i.d.	oral, b.i.d.
Preoperative doses (mg, range)	300-1600	100-300
Daily dose (mg, range) used in acute pain	1800-3600	225-600
Dose adjustment according to renal function	Yes	Yes
Duration of treatment in the studies	7 days	7 days
Opioid sparing effect (% decrease from control group)	20-62	16-60
Main adverse effects	Dizziness (20%) Sedation (20-30%)	Same as gabapentin

t.i.d. = three times daily; b.i.d. = twice daily

In a recent systematic review performed by Clarke et al. (241), the administration of the perioperative gabapentinoids showed promising results. Out of eight trials, four found that gabapentin decreased the occurrence of chronic pain after more than two months. However, to blunt the peripheral and central sensitization processes that begin during surgery, it was necessary to give a rather high preoperative dose of 1200 mg and to continue pharmacological therapy into the postoperative phase. All three pregabalin trials demonstrated that pregabalin decreased chronic postsurgical pain, and two of those trials also reported an improvement in postoperative patient function. In the two trials involving lumbar discectomy (242) and total knee arthroplasty (243), a dose of 300 mg was given as premedication before surgery and then 25-150 mg twice daily for 2-14 days after surgery. The third pregabalin trial studied elderly patients who were undergoing cardiac surgery, and the dose for these patients was 150 mg preoperatively, then continuing 75 mg twice daily for 5 days (244). Due to its more reliable absorption profile, pregabalin is considered to be more promising than gabapentin in this type of surgery. These findings were confirmed by a meta-analysis that concluded that there was an overall moderate-to-large reduction in chronic postsurgical pain (241).

6.5.3. WHICH SURGICAL PATIENTS COULD BENEFIT FROM PERIOPERATIVE GABAPENTINOIDS?

Currently, gabapentinoids are not officially recommended for acute perioperative pain. They also have adverse effects that may delay the ambulatory patients' discharge from hospital. Furthermore, a screening tool or diagnostic test that can preoperatively identify the patients at risk of developing severe acute or chronic postsurgical pain (see Discussion 6.4.) is urgently needed. Gabapentinoids might be beneficial if the patient is scheduled to undergo major surgery that may involve a risk of nerve damage (for example, thoracotomy, mastectomy with axillary node dissection, limb amputation, spinal surgery, large facial and neck dissections), or he/she has a pre-existing chronic pain. Additionally, gabapentinoids can be an integral part of multimodal analgesia if the patient has difficulties in tolerating opioids and benefits from the opioid-sparing effect (for example, elderly people, obese patients with sleep apnoea, or opioid addicts).

Free-floating anxiety disorder is an official indication for gabapentinoids, and they have been studied as an anxiolytic premedication before surgery with some promising results (see chapter 6.5.1.). Anxiety is one of the main risk factors for acute and persistent postoperative pain, and gabapentinoids could, therefore, be utilized as adjuvant analgesics perioperatively with these psychologically vulnerable patients (see chapters 2.5.1 and 6.4., Table 4).

Some evidence suggests that pregabalin attenuates opioid-induced hyperalgesia that is caused by remifentanil during surgery. After laparoscopic urologic surgery as well as open abdominal hysterectomy surgery, when remifentanil was administered during the procedure, pregabalin doses of 150-300 mg have decreased pain intensity, the area of hyperalgesia and the mechanical hyperalgesia threshold (245, 246). Therefore, patients anaesthetised with the common propofol-remifentanil infusions may benefit from preoperative gabapentinoids, especially after painful operations such as a thoracotomy.

Due to a greater bioavailability, pregabalin is superior to gabapentin, and the doses of pregabalin should be sufficiently high: 100-300 mg preoperatively as premedication (depending on renal function), continuing with 225-600 mg/day postoperatively (see Table 10). However, definitive recommendations for the dosing and the duration of the therapy for gabapentinoids postoperatively cannot be provided without further research, and cautious use of these adjuvants is still warranted.

6.6. LAPAROSCOPIC CHOLECYSTECTOMY AS A DAY SURGERY OPERATION

Laparoscopic cholecystectomy would appear to be an ideal operation for ambulatory surgery because the duration of the surgery is short, the incisions are small, the rate of immediate complications is low, and the gastrointestinal homeostasis is maintained. Despite this, reports show up to 37% of unplanned overnight admissions (1). The results of Study II demonstrated that 95% of the LCC patients scheduled for outpatient surgery could be operated on a day-case basis. Smooth ambulatory LCC was enabled by using a PONV-preventing anaesthetic technique with multimodal pain treatment by making the most of opioid-sparing drugs, such as perioperative dexamethasone, NSAIDs or paracetamol and local anesthetics.

Surprisingly, paracetamol was found to be as effective as the coxibs in the treatment of pain after LCC. This could be due to the visceral nature of post-LCC pain quite resistant to NSAIDs and longer elimination half-life of valdecoxib than paracetamol relative to the small dose of 40 mg daily (254, 255). Additionally, the role of a placebo effect cannot be ignored, when paracetamol was taken four times a day compared with once daily intake of coxib. Dexamethasone decreased the need for oxycodone in Phase 2 PACU (2-5 hours after surgery) and should most likely be administered earlier, for example, at the induction of anaesthesia. Optimally, dexamethasone should be administered one to two hours before surgery (140), which may be difficult to perform when the patients arrive at the hospital just prior to their operation. Furthermore, glucocorticoids have also been found to possess more rapid non-genomic effects, which makes the timing of their administration less important (141).

Dexamethasone is one of the most potent and longest-acting corticosteroids available, with a biologic half-life of 36-72 hours. Murphy et al. (247) reported that a single preoperative 8 mg dose of dexamethasone improved the emotional and physical state of patients, and also alleviated pain on the day following surgery. However, Study II found no difference in pain intensity at home between the patients who were treated with or without dexamethasone. This discrepancy may be explained by the multimodal analgesic regimen that was utilized in Study II, but not in the study by Murphy et al.

On the first postoperative day and continuing for several days at home (see Figure 2/Study II), the referred pain in the right shoulder was suggested to be the most common and intense. This disabling pain was more severe and longer-lasting than described in other studies, although a rather low-pressure pneumoperitoneum (<12 mmHg) was used. To prevent shoulder-tip pain after LCC, it may be that the pressure of CO_2 insufflation should be as low as 8 mmHg (248).

6.6.1. THE OPTIMAL ANALGESIC METHOD FOR DAY-CASE LCC PATIENTS

Invasive pain treatment techniques, such as epidural analgesia, are not suitable for ambulatory LCC. Based on the current literature (249, 250) and on Study II in this thesis, the analgesic regimen could include a single preoperative or intraoperative dose of dexamethasone 8-10 mg (251), incisional and intraperitoneal local anaesthetics, avoidance of drains, and the regular use of NSAIDs or COX-2 inhibitors during the first 3-4 postoperative days, possibly starting preoperatively. Due to the side effects, prophylactic treatment with postoperative opioids is not recommended, but short-acting opioids can be used on demand when needed. Other opioid-sparing adjuvants, such as gabapentinoids or NMDA receptor antagonists, cannot be recommended for day surgery without large dose-response studies (2, 252).

6.7. ADVERSE EFFECTS OF PERIOPERATIVE NSAIDS

In Study IV, the patient levels of S-creatinine or cystatine-C before and after thoracotomy were not elevated, and there were no differences in adverse effects (for example, differences in urine output, blood loss, or gastrointestinal problems) between the pare-/valdecoxib, diclofenac and epidural groups. However, this study was underpowered to detect these differences. In Study II, valdecoxib also did not cause any serious adverse effects with the day-case LCC patients. Only one patient had to discontinue the use of the coxibs at home due to that patient developing a flushed face.

Coxibs have been reported to increase the risk of thromboembolic complications after coronary artery bypass grafting (CABG) in patients with atherosclerotic disease (73), but not after non-cardiac surgery (74, 75). The inhibition of COX-2-dependent, vasoprotective prostacyclin without a complete suppression of COX-1-dependent platelet function might play a role in their cardiovascular toxicity. However, it is now understood that, depending on the extent of inhibition of COX-2, all NSAIDs (as well as those that are non-selective) are associated to a varying degree with cardiovascular risks (253).

In conclusion, coxibs have very few adverse effects when administered for a short period of time to young, healthy patients with no pre-existing thromboembolic risk factors.

6.8. THE EFFECT OF PARACETAMOL AND TROPISETRON ON EXPERIMENTAL PAIN

The demand for opioid-sparing adjuvant drugs after surgery is rapidly growing. Because NSAIDs are contraindicated in elderly patients and in patients who are at risk for gastrointestinal bleeding, cardiovascular problems, or renal insufficiency, there is a need for postoperative paracetamol. In addition, 5-HT3 antagonists, setrons, are commonly administered to prevent or manage postoperative and chemotherapy-induced nausea and vomiting. Laparoscopic cholecystectomy is a typical day-case operation with an increased chance of PONV, which jeopardizes the discharge of the patients on the day of surgery. For this reason, these patients are premedicated with setrons and treated postoperatively with paracetamol, as they are in Study II. Assuming that setrons would abolish the analgesic action of paracetamol, the daily clinical management of postoperative pain would need a complete reassessment. This hypothesis was the basic objective for conducting Study V.

In Study V, 2 g of IV paracetamol alone did not induce a measurable analgesic effect in the cold pressor, heat pain or electrical pain stimulation tests. It is noteworthy that Pickering et al. (29, 30) could demonstrate the analgesic action of paracetamol in mechanical and electrical pain stimulation tests, with an *oral* dose of 1 g. In Study V, after calculating the sensory and pain scores as a percentage of the individual score at baseline (as Pickering et al. did), tropisetron seemed to *amplify* the analgesic action of paracetamol, which is an another fundamental difference between these experimental trials (see Fig 3/Study V). The results from Study V agree with the evidence from basic research and clinical studies, indicating that 5-HT3 receptor antagonists may have analgesic properties.

Paracetamol is difficult to investigate in experimental pain models, since its mechanism of action is still unknown. In two recent reviews, Staahl et al. (113) and Olesen et al. (114) concluded that the analgesia from paracetamol is difficult to detect with traditional pain stimulation tests. The suggestion is that instead of subjective pain ratings, the analgesia should probably be assessed by adopting extremely sensitive methods, such as evoked brain potentials or EEG. Intravenous (but not oral) paracetamol has been shown to reduce central hyperalgesia in continuous intracutaneous electrical stimulation tests without any effect on ongoing pain. However, this antihyperalgesic effect of paracetamol remains controversial (see Table 1/Study V). The pain stimulation tests in Study V caused short-term pain that did not induce any central sensitization, which is a possible reason for a lack of the analgesic effect of paracetamol.

The reason for paracetamol and tropisetron having a weak analgesic effect as sole agents but not when administered together, might reside in the complex interaction of the central serotonergic pain pathways (95). The combination of these drugs could

be pronociceptive, enhancing the pain signal at the spinal level, or there could be a pharmacokinetic interaction between them. Neither Study V nor the experimental trials of Pickering et al. detected an analgesic effect of tropisetron.

The setrons did not affect the analgesic action of paracetamol in clinical studies (93, 94). Before conducting further experimental studies that explore the possible interaction between these universally administered drugs, it would first be necessary to establish the pain models that reliably demonstrate an analgesic effect of paracetamol. Furthermore, the possible intrinsic analgesic action of 5-HT3 antagonists cannot be ignored. At this point, however, there is no need to avoid the concomitant administration of paracetamol and setrons.

7. LIMITATIONS OF THE PRESENT STUDIES

Due to some limitations, the results of the studies presented in this thesis must be interpreted with caution.

Study I was not randomized or controlled, because the anaesthesiologist in charge selected the method of pain relief. Furthermore, this study used predominantly descriptive statistics. However, the Student's t-test was utilized when applicable. Since the number of patients in the IV-PCA group was small (n=18) and the study lacked a randomization and standardization of the pain therapy, it was not possible to calculate the statistical comparisons between the treatments.

The activation of the metabolic response to surgery begins immediately after the incision, and due to genomic changes, the onset of the action of glucocorticoids takes 1-2 hours (140). In **Study II,** dexamethasone was administered 30 minutes before the end of surgery, and the maximum effect seemed to appear after 2-5 hours just before the patient's discharge from hospital. Had dexamethasone been administered earlier at the induction of anaesthesia, there might also have been less pain in PACU 1. However, glucocorticoids may also show more rapid effects through membrane receptors (141).

In Study II there may be several reasons why more patients treated with coxibs needed rescue analgesics at home compared with patients treated with paracetamol. The visceral pain which involves the autonomic nervous system may be quite resistant to NSAIDs alone. The t½ of valdecoxib is 8 h, and the steady-state plasma concentrations are reached by day 4 (254), whereas the t½ of paracetamol is 2 h. Therefore, the greatest benefit from valdecoxib may not have been experienced in time. Puolakka et al. (255) reported that a 40 mg dose of parecoxib is not effective for early postoperative pain after LCC, and doubling the dose improved analgesia. Thus it might have been more effective to administer 40 mg of valdecoxib to these healthy patients twice per day for 3-4 days at home. Paracetamol was taken four times a day compared with the once per day intake of coxib. Therefore, there may have also been a placebo effect, which could have been avoided by giving three placebo tablets in addition to the one valdecoxib tablet per day.

In Study II, tropisetron was administered to all patients and consequently, the speculated interaction between paracetamol and the 5-HT3 antagonists could not be analyzed (29, 30).

In **Study III,** no conclusions can be drawn on the optimal dose and duration of the postoperative treatment with gabapentinoids owing to the heterogeneous data in the studies.

Study IV is underpowered: the intended sample size was not attained and the study had to be prematurely interrupted because valdecoxib was withdrawn globally

in 2005. At the same time, open thoracotomies were becoming increasingly rare due to thoracoscopic operations. A prospective, non-standardized control group consisting of those patients who did not meet the inclusion criteria for the study and who were receiving current standard pain management in the clinic, was used as a control group and the data, apart from the questionnaire data, were naturally not collected in as they were in the intervention groups. The control patients had more cardiovascular and pulmonary diseases than the intervention patients. Statistically, this study adopted analytical methods that were primarily descriptive and non-parametric. However, the minimum number of patients per study arm which is accepted in the individual studies for systematic reviews, is 10 patients (209).

In **Study V**, the electrical stimulus (Pain Matcher) was identical with that of Pickering's (29), but the cold pressor test displayed slight differences. It was still validated, and these small differences cannot explain the differences between the results of Study V and Pickering's findings. These experimental studies included only male volunteers, whereas the clinical studies included both genders (93, 94). This factor is relevant because the prevalence of the most common forms of pain seems to be higher among women than men, and women also report greater pain after invasive procedures and after experimentally induced pain. Men may exhibit greater DNIC (see 2.5.1.) than women, and this phenomenon may be particularly predictive of clinical pain (256). Future studies on the effects and interactions of paracetamol would be useful to be conducted separately for men and women.

It is possible that the thermal and electrical stimulation tests in Study V could not detect the analgesic effect of paracetamol because the short duration of pain did not induce central sensitization. Unfortunately, the interaction between paracetamol and tropisetron could not be assessed.

8. CLINICAL IMPLICATIONS AND FUTURE ASPECTS

Acute and chronic postoperative pain remains a challenge, particularly when patients are currently discharged much earlier than they were previously. Most clinical studies that report acute pain after surgery focus on the acute phase when patients are still in hospital, and there are limited data about the sub-acute phase at home. This phase is important because central sensitization continues, predisposing the patients to persistent pain. This thesis presents information on the intensity of the acute postoperative pain, on the occurrence of chronic post-thoracotomy pain as well as the pain experienced during the first week after being discharged from hospital. During the first week at home, over 70% of the patients seemed to require weak opioids on a daily basis. To prevent persistent post-thoracotomy pain, the extended protocol for high quality pain management in hospital covering also the sub-acute phase at home, was important. These studies also provide some evidence that safe and effective alternatives to thoracic epidural analgesia do exist and that these deserve further research.

It seems that standard care is not sufficient to prevent chronic post-thoracotomy pain. The idea to include the standard "as usual" care patients as a control group and to compare them with the intervention patients is rather new and it deserves further consideration in future studies.

By identifying the patients at risk of severe postoperative acute and chronic pain, this will allow us to individually tailor their pain management, avoiding unnecessary invasive methods. At present, all patients are not seen by the anaesthesiologist on the day before their surgery. An electronic questionnaire surveying preoperative risk factors of acute and persistent pain could be a means to identify the patients who would benefit most from invasive and multimodal pain treatment. Postoperatively, patients could be earmarked as to who would benefit from a longer and closer follow-up. This identification could be the screening of hyperalgesia by using simple measures, such as "a coughing test" and by recording pain intensity and analgesic consumption by the APS. These patients could be seen by anaesthesiologists one to three weeks after the surgery in a postsurgery APS follow-up outpatient clinic and this would be a new "bridge" between APS and a chronic pain clinic.

The analgesic regimen for ambulatory LCC patients could include a single dose of opioid-sparing dexamethasone, incisional and possibly intraperitoneal local anaesthetics, as well as regular NSAIDs or COX-2 inhibitors during the first 3-4 postoperative days. Coxibs were found to be safe when administered to young and healthy patients for a short period of time.

The opioid-sparing and pain alleviating role of the gabapentinoids in acute pain after surgery was demonstrated in a systematic review. However, acute

postoperative pain is not yet an official indication for gabapentinoids. This thesis offers some suggestions for clinicians regarding the patients who could benefit from perioperative gabapentinoids. However, definitive recommendations for the dosing and duration of gabapentinoid therapy need to be evaluated in future research.

It was previously suggested that tropisetron abolishes the analgesic effect of paracetamol, and some clinicians have avoided concomitant administration of these common drugs. However, the analgesic action of paracetamol was impossible to detect in experimental tests with subjective pain measure outcomes, and thus no conclusions about the interaction can be drawn. To conduct experimental studies investigating paracetamol and setrons, pain models that reliably show the analgesic efficacy of paracetamol need to be established. Furthermore, the possible intrinsic analgesic action of 5-HT3 antagonists should be taken into account. Currently, paracetamol and setrons can be administrated together.

To be able to design clinical studies of persistent post-surgical pain, researchers need a better understanding of the mechanisms and risk factors that are involved in chronic pain, and the follow-up studies must be sufficiently long-term. For future research in preventing and treating chronic pain, hyperpolarization-activated cyclic nucleotide-modulated ion channels (HCN type 2) have recently been found to serve as a link between inflammatory and neuropathic pain, and selective HCN2-blockers might also be an interesting topic (257, 258). Whereas relevant demographic, psychosocial and pain-related risk factors as well as genetic factors, and some experimental tests such as temporal summation, DNIC (CPM) and electrical stimulation are involved in acute and chronic pain, they are not yet clinically practical.

9. CONCLUSIONS

1. The incidence of persistent post-thoracotomy pain after 6 months was 3-24% in the past decade.

2. Persistent post-thoracotomy pain was more prevalent among the control patients who were treated with standard care than the intervention patients involved in the study. The acute pain intensity between these groups was similar. However, the pain management and follow-up of the trial participants differed substantially from those of standard "as usual" care patients. A comparison of the outcomes between these groups is informative, and this data can be utilized to improve pain management protocols.

3. Although patient controlled epidural analgesia (PCEA) was associated with less movement-related pain, both PCEA and IV-PCA morphine provided sufficient analgesia and a low incidence of persistent post-thoracotomy pain, without major adverse effects. For epidural versus IV-PCA+NSAIDs, the intensity of dynamic pain during physiotherapy was less and the duration of pain after coughing was shorter. However, TEA cannot be used in every patient, and a valuable alternative may be the IV-PCA + NSAIDs with a strict follow-up.

4. For pain after ambulatory LCC, paracetamol was as effective as pare-/valdecoxib. Dexamethasone decreased the need for oxycodone in Phase 2 PACU, and its effect was similar to the effect on patients who were treated with paracetamol and coxibs. However, compared to those administered paracetamol, more patients treated with coxibs needed rescue medication at home. An appropriate anaesthetic technique with multimodal pain management enabled smooth outpatient LCC in 95% of the study patients.

5. To prevent acute and persistent post-thoracotomy pain, high quality pain management in the acute phase that is also extended to the patient's home for the first week after discharge could be more important than any analgesic method *per se*. More attention needs to focus on the regular follow-up of the patients during the sub-acute phase at home, especially to those at risk of chronic postoperative pain. Moreover, almost half of the LCC patients required some analgesic medication one week after discharge. For these patients, shoulder pain was also common and intense for several days at home.

6. Gabapentinoids effectively reduce postoperative pain, opioid consumption (20-62%) and opioid-related adverse effects postoperatively, with negligible adverse effects of their own. Thus far, due to the heterogeneity of the studies, conclusions cannot be drawn on the optimal dose, the duration of the treatment, and the long-term benefits of perioperative gabapentinoids.

7. Paracetamol did not display a measurable analgesic effect in the thermal or electrical pain stimulation tests. Therefore, no conclusions can be drawn regarding any possible interaction between paracetamol and tropisetron. To design further experimental studies on this drug, pain models should be established that reliably show an analgesic effect of paracetamol. Furthermore, when studying the interactions between paracetamol and 5-HT3 antagonists the possible intrinsic analgesic effect of tropisetron should not be ignored. Thus far, there is no firm evidence to suggest that the use of setrons with paracetamol should be avoided.

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APPENDIX 1

Dear Madam/Sir
You had a lung operation about 6 months ago in Meilahti Hospital. We enquired after Your health by telephone one week after discharge from hospital, and by a questionnaire three months after that. Now after six months we would still like to know how You are, and we would appreciate if You would kindly answer the following questions.

We ask Your pain with Visual analogue scale.

1. If You have any pain around the scar, please mark a cross to this VAS line (X):

a) Your pain at rest

_____
no pain (0) worst imaginable pain (10)

b) Your pain when breathing deeply

_____
no pain (0) worst imaginable pain (10)

c) Your pain when coughing

_____
no pain (0) worst imaginable pain (10)

2. Is Your pain around the scar

__ mild

__ moderate

__ severe

__ excruciating

__ no pain

3. If You still have pain around the scar, do You feel it

____ all the time

____ not all the time, but daily

____ a few times a week

____ a few times a month

____ only in specific situations, please name them_____

_____

4. If You do not have pain any more, for how long did it continue after discharge from hospital?

____ less than 3 weeks

____ 3 weeks – 2 months

____ 2 months – 5 months

____ more than 5 months but not any more

5. Do You have pain, numbness or other symptoms elsewhere than around the scar, which might be due to the operation?

____ yes

____ no

If "yes", please specify: _____

_____

6. If You still have pain around the scar, which of the following activities make it worse?

____ I feel pain also at rest

____ getting up from the bed

____ standing

____ walking

____ weather changes

____ feeling depressed

____ carrying things with the arm on the operated side

____ combing hair with the arm on the operated side

____ some other activity: _____

_____

7. Does the pain make Your daily activities more difficult (e.g. clothing yourself, making bed)?

____ not at all

____ a little

____ moderately

____ quite a lot

____ very much

If it does, please specify how: _____

_____

8. Does the pain interfere with Your sleep?

____ yes

____ no

If it does, how often?

____ every night

____ a few times a week

____ less frequently

9. Have You used pain medication at home for the pain around the scar?

____ yes, daily

____ yes, a few times a week

____ yes, a few times a month

____ no, I have not

If “yes”, please specify which medication: _____

_____

Please name also other medication You use daily (e.g. sleeping pills, antidepressants):

_____

_____

10. Have You received some other treatment than medication for Your pain (e.g. local anaesthesia, physiotherapy)?

_____

_____

11. Have these medications or other treatments been effective for Your pain?

____ not at all

____ a little

____ moderately

____ quite a lot

____ very much

12. Has the intensity of Your pain around the scar changed with time?

____ yes, it has intensified

____ yes, it has diminished

____ it has remained the same

____ no pain any more

13. Have You contacted the hospital because of postoperative problems? Please specify:

_____

_____

14. Have You gone through cytostatic or radiotherapy?

_____

_____

15. Please draw Your pain areas in the picture enclosed.

If You want to tell something else about Your pain, please write it here or on the other side of the paper.

Many thanks for Your trouble!

Elina Tiippana
anaesthesiologist
tel: 4711*

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anaesthesiologist
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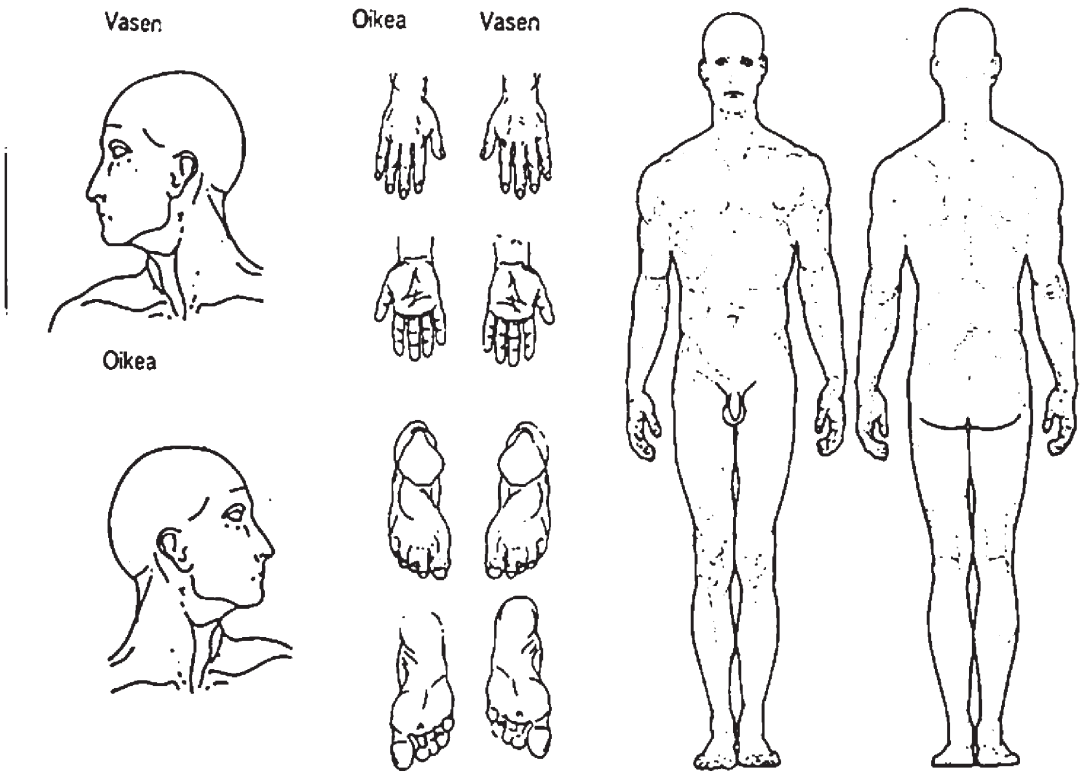
1. Missä kipunne tuntuu? Merkitkää kuvaan kaikki paikat, joissa tunnette kipua
Kayttäkää kipualueiden merkitsemisessä apuna seuraavia merkkejä kuvaamaan kivun luonnetta.

Särky XXXXXXXX (piirtäkää rasteilla) **Aristava kipu** = = = = == (piirtäkää poikkiviivalla)

Polttava kipu oooooooo (piirtäkää ympyröillä) **Tunnottomuus** |||||||||||||| (piirtäkää pystyviivoilla)



Translation:

1. Where is Your pain? Please draw each area in Your body where You have pain. Please use the following symbols to describe the nature of the pain.

Ache (XXXX) Tenderness (=====)

Burning pain (oooo) Numbness (||||)

vasen = left oikea = right

APPENDIX 2

Patient number_____

1. postoperative day,
after the telephone interview

Pain during the day, time_____p.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement (breathing deeply, coughing, activities)

_____

0 10
no pain worst imaginable pain

Pain in the evening before going to sleep, time_____p.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement

_____

0 10
no pain worst imaginable pain

Where is the pain?_____

Please describe the nature of the pain? _____

_____

5) Pain medication during 24 hours (analgetics, doses, times): _____

_____

_____

6) Adverse effects from the analgetics?_____

_____

_____

2. postoperative day

Pain on the morning, time_____a.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement (breathing deeply, coughing, activities)

_____

0 10
no pain worst imaginable pain

Pain during the day or evening, time_____p.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement

_____

0 10
no pain worst imaginable pain

3) Where is the pain?_____

4) Please describe the nature of the pain? _____

5) Pain medication during 24 hours (analgetics, doses, times): _____

_____

_____

6) Adverse effects from the analgetics? _____

_____

3. postoperative day

1) Pain on the morning, time_____a.m.

pain at rest

_____

0 10

no pain worst imaginable pain

pain at movement (breathing deeply, coughing, activities)

_____

0 10

no pain worst imaginable pain

2) Pain during the day or evening, time_____p.m.

pain at rest

_____

0 10

no pain worst imaginable pain

pain at movement

_____

0 10

no pain worst imaginable pain

3) Where is the pain?_____

4) Please describe the nature of the pain? _____

_____

_____

5) Pain medication during 24 hours (analgetics, doses, times): _____

_____

_____

6) Adverse effects from the analgetics? _____

_____

_____

4. postoperative day

1) Pain on the morning, time_____a.m.

pain at rest

_____

0 10

no pain worst imaginable pain

pain at movement (breathing deeply, coughing, activities)

_____

0 10
no pain worst imaginable pain

2) Pain during the day or evening, time_____p.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement

_____

0 10
no pain worst imaginable pain

3) Where is the pain?_____

4) Please describe the nature of the pain? _____

_____

_____

5) Pain medication during 24 hours (analgetics, doses, times): _____

_____

_____

6) Adverse effects from the analgetics? _____

_____

_____

5. postoperative day

1) Pain on the morning, time_____a.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement (breathing deeply, coughing, activities)

_____

0 10
no pain worst imaginable pain

2) Pain during the day or evening, time_____p.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement

_____

0 10
no pain worst imaginable pain

3) Where is the pain?_____

4) Please describe the nature of the pain? _____

_____

_____

5) Pain medication during 24 hours (analgetics, doses, times): _____

_____

_____

6) Adverse effects from the analgetics? _____

_____

_____

6. postoperative day

1) Pain on the morning, time_____a.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement (breathing deeply, coughing, activities)

_____

0 10
no pain worst imaginable pain

2) Pain during the day or evening, time_____p.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement

_____

0 10
no pain worst imaginable pain

3) Where is the pain?_____

4) Please describe the nature of the pain? _____

_____

_____

5) Pain medication during 24 hours (analgetics, doses, times): _____

_____

_____

6) Adverse effects from the analgetics? _____

_____

_____

7. postoperative day *(NB: the questionnaire is a little different from the previous ones)*

1) Pain on the morning, time_____a.m.

pain at rest

_____

0 10
no pain worst imaginable pain

pain at movement (breathing deeply, coughing, activities)

_____

0 10
no pain worst imaginable pain

2) Pain during the day or evening, time_____p.m.

pain at rest

_____

0 10

no pain worst imaginable pain

pain at movement

_____

0 10

no pain worst imaginable pain

3) Where is the pain?_____

4) After the operation, when did you feel well enough to manage the daily activities normally (dressing, doing the dishes, outdoor activities etc.)? _____

_____

5) Do you feel fit for work one week after the operation?

__ yes

__ no;

If "no", please specify why? _____

_____

If You like to comment, please write here or on the other side of the paper.

Many thanks for Your trouble!